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

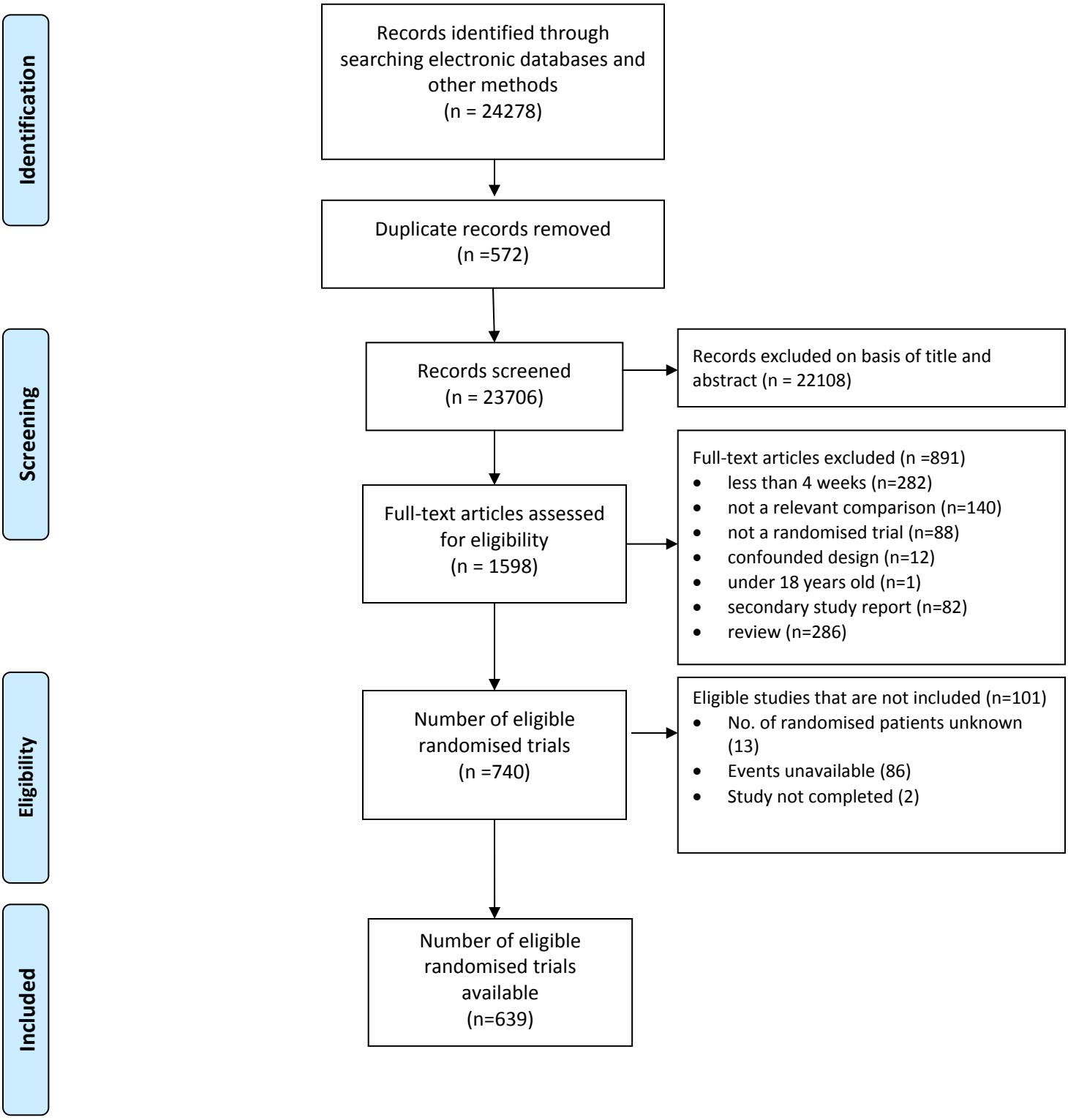
	Overall	Coxib vs placebo	tNSAID vs placebo	Coxib vs naproxen	Coxib vs other tNSAID
No. randomised	192981	73635	18018	42222	84680
No. trials	157	113	47	34	54
Age, years	61.2 (11.3)	60.1 (12.4)	59.7 (13.6)	60.6 (11.3)	61.6 (10.6)
Female, %	68	59	67	73	73
Caucasian, %	79	82	72	76	77
Indication for treatment, %					
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

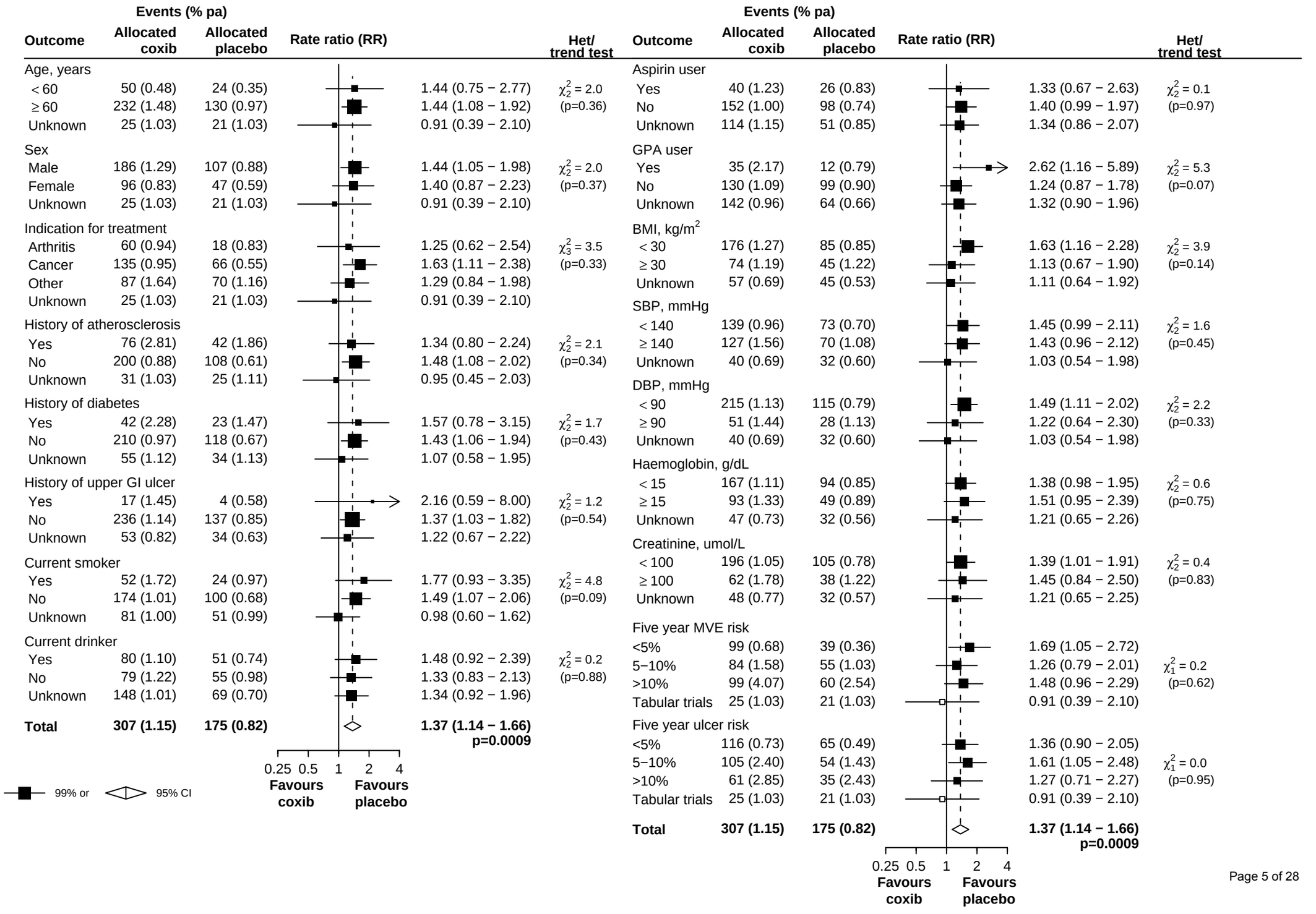
Webtable 3: Effects of coxibs and tNSAIDs on major vascular events and upper GI complications

	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)

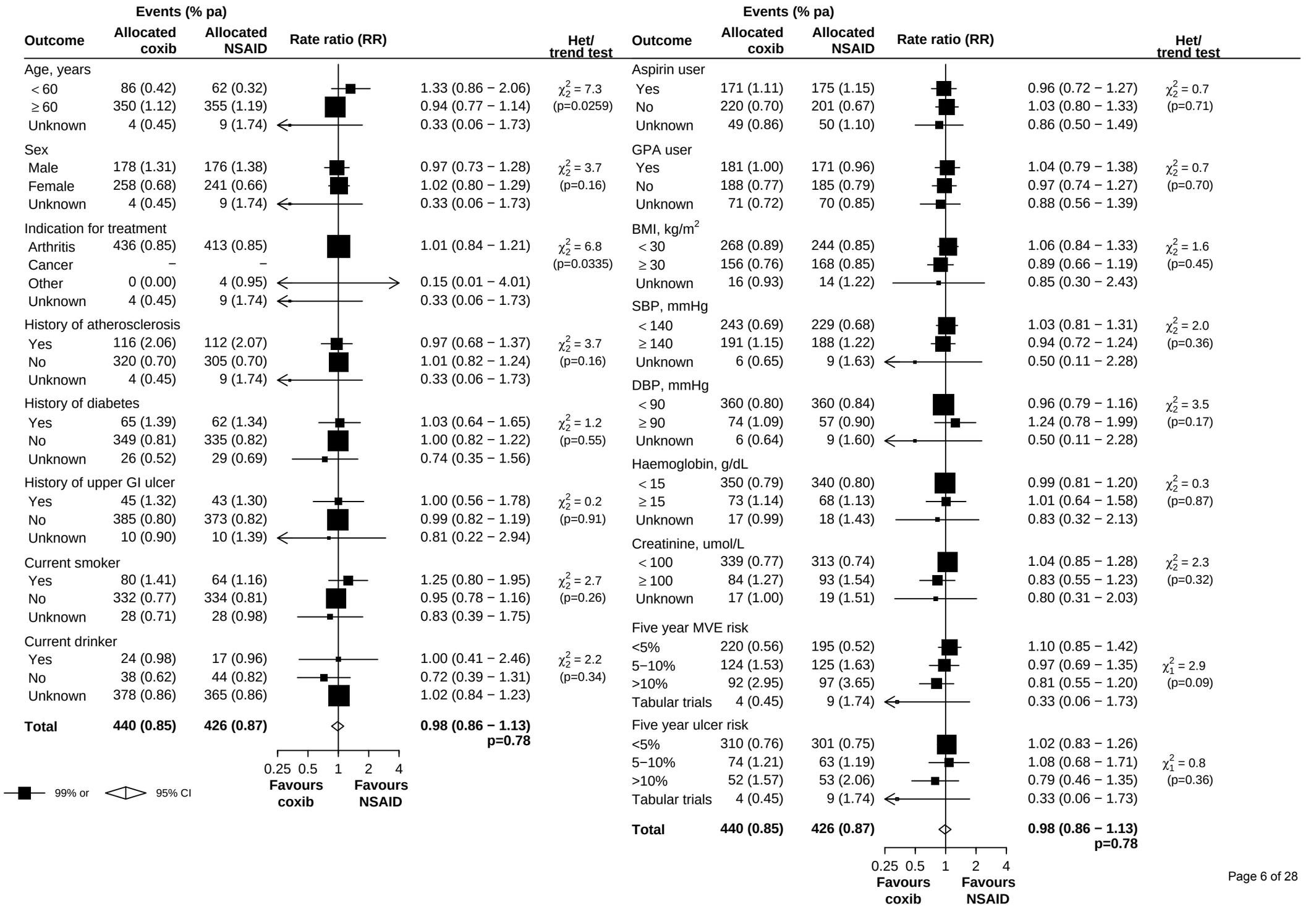
Webfigure 1: PRISMA flow diagram



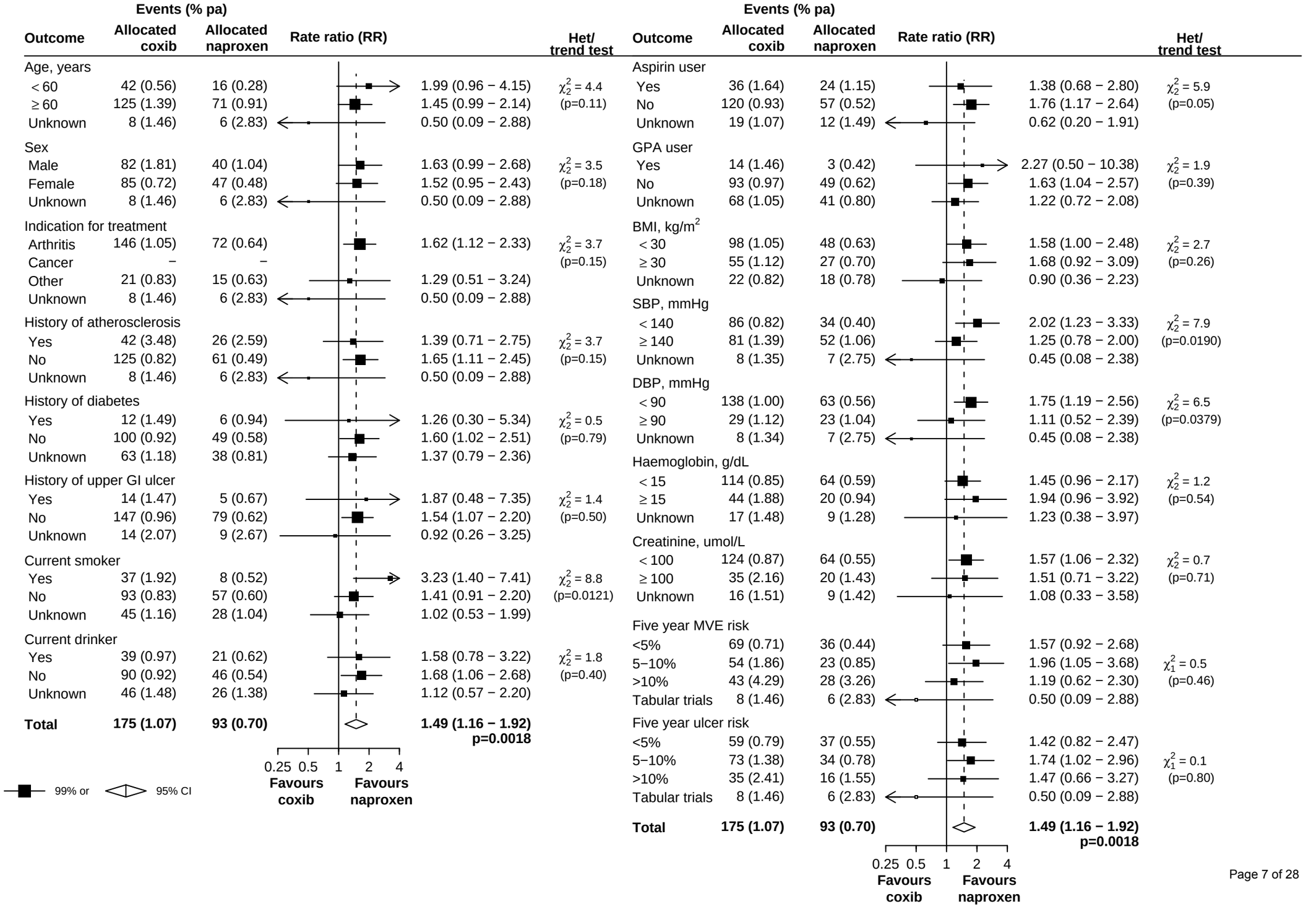
Webfigure 2: Effect of coxib therapy on major vascular events, by baseline characteristics



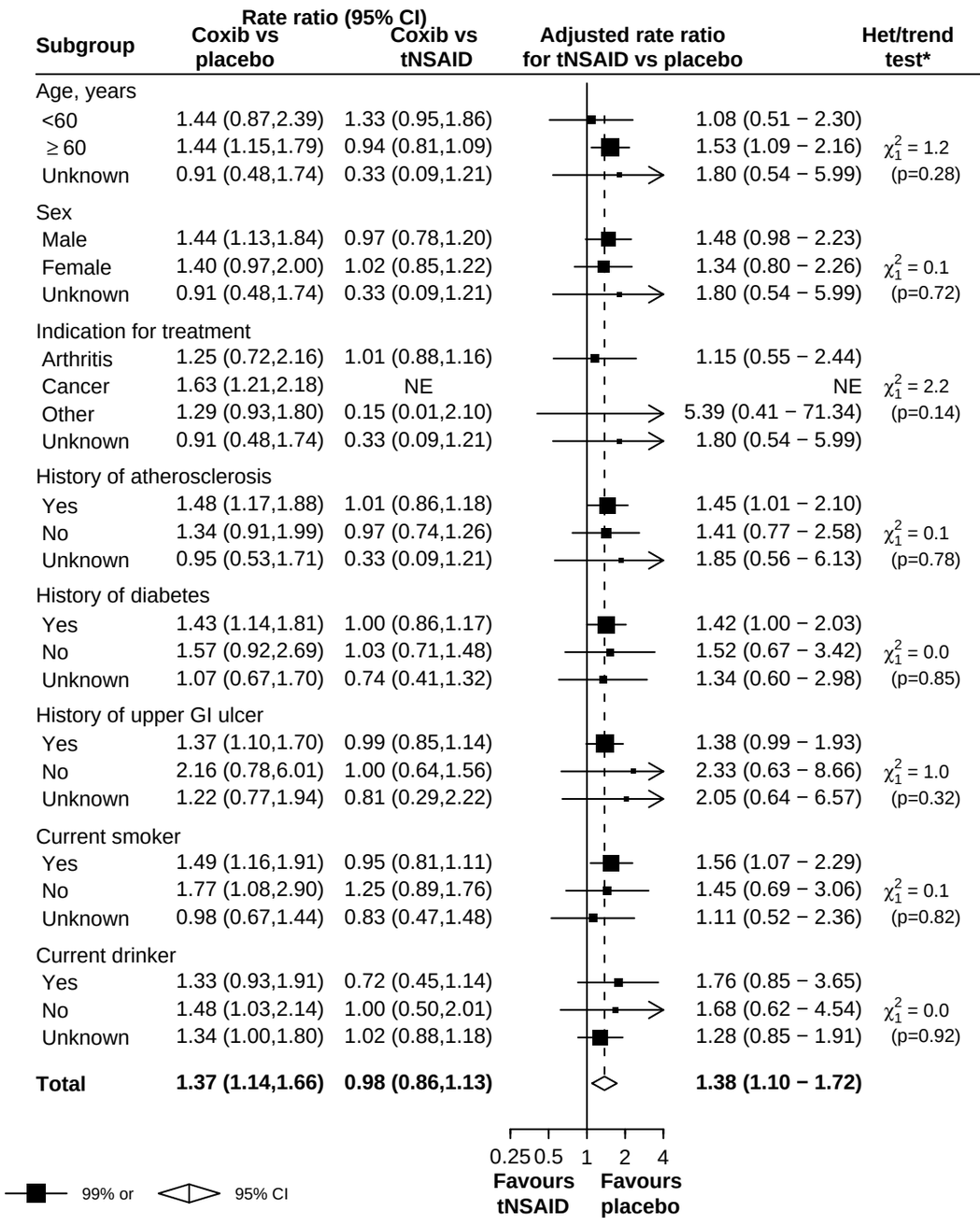
Webfigure 3: Comparisons of coxibs vs non−naproxen NSAIDs. Effect on major vascular events by baseline characteristics

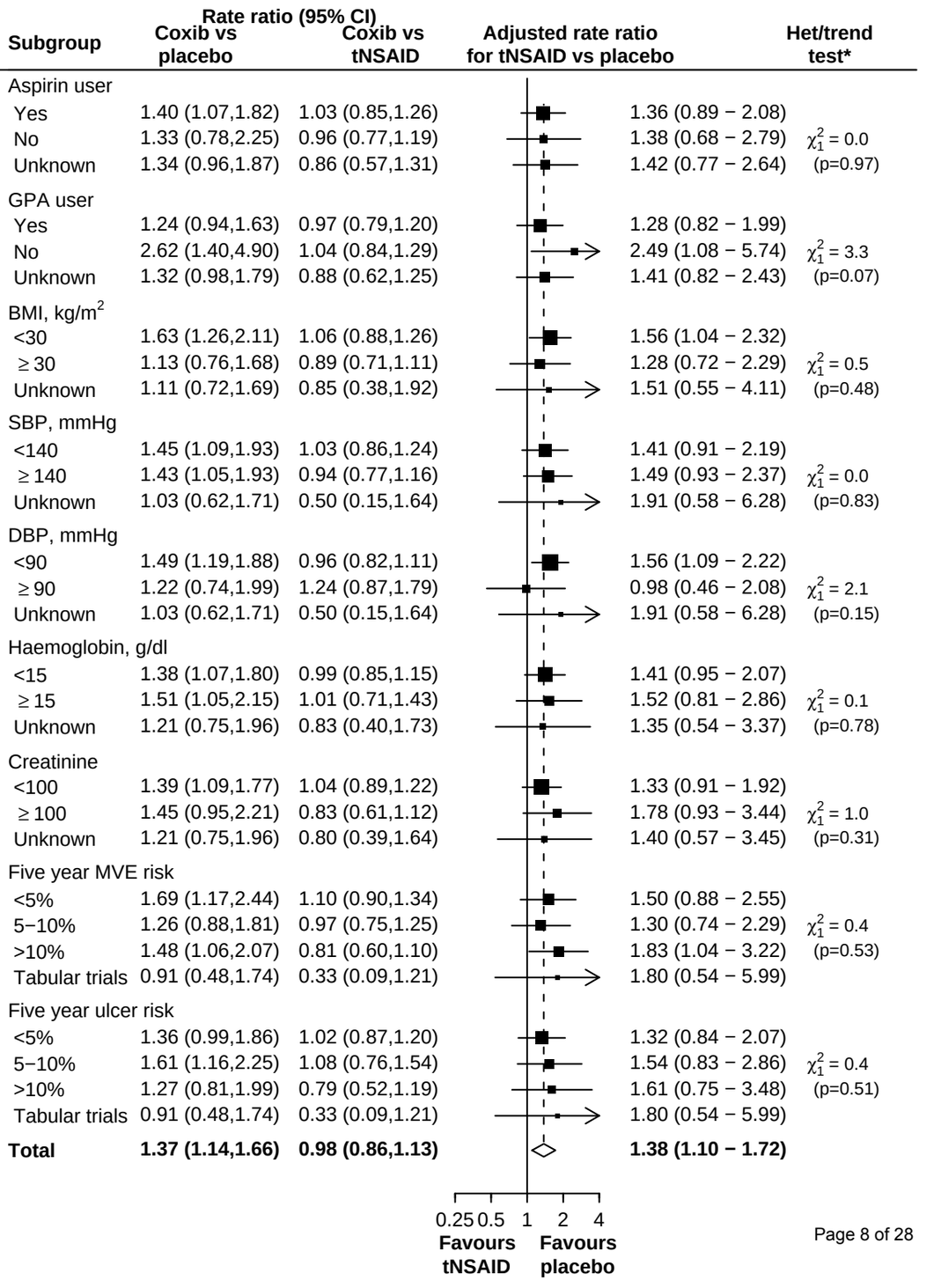


Webfigure 4: Comparisons of coxibs vs naproxen. Effect on major vascular events by baseline characteristics



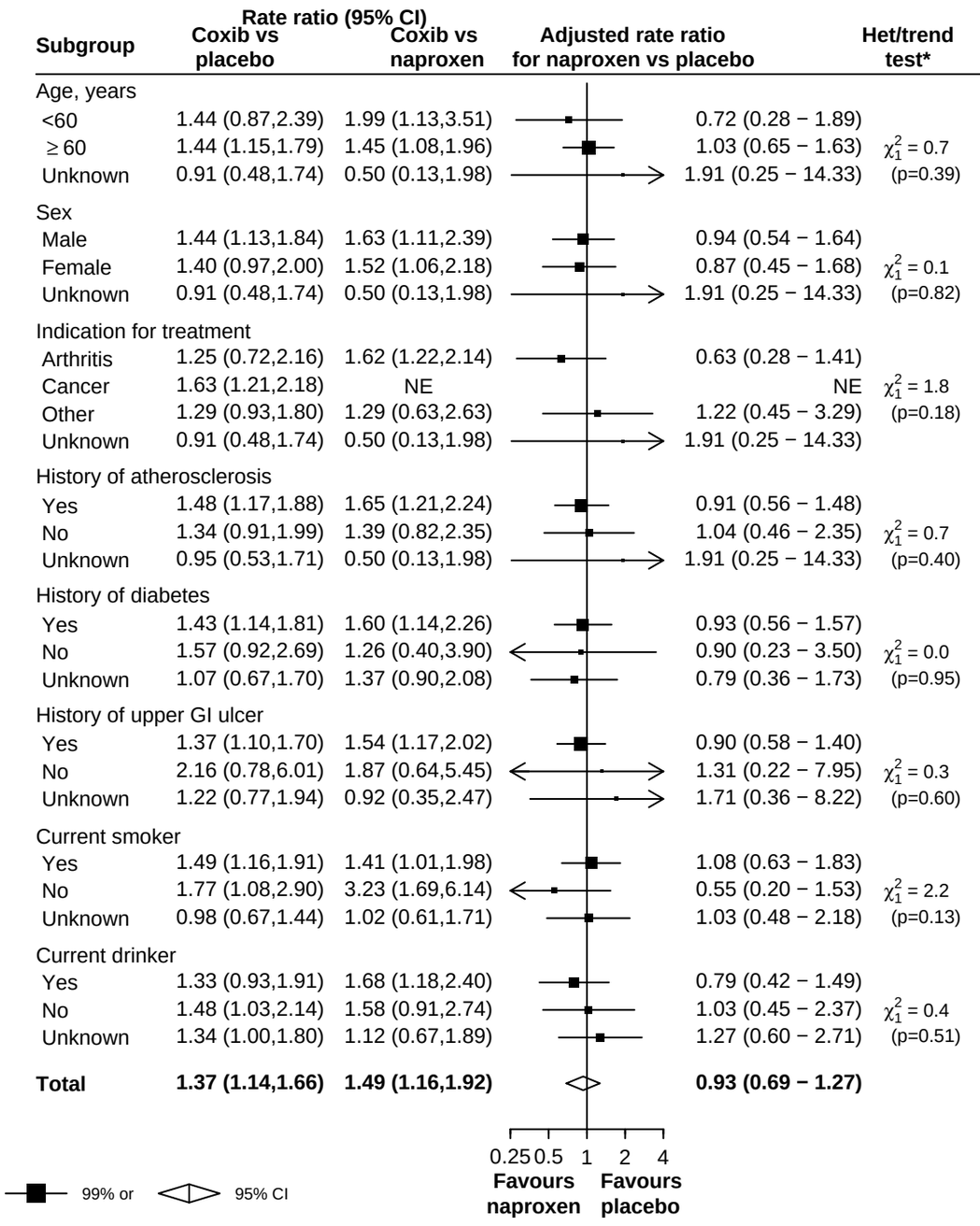
Webfigure 5: Effect of non−naproxen tNSAIDs on major vascular events, by baseline characteristics

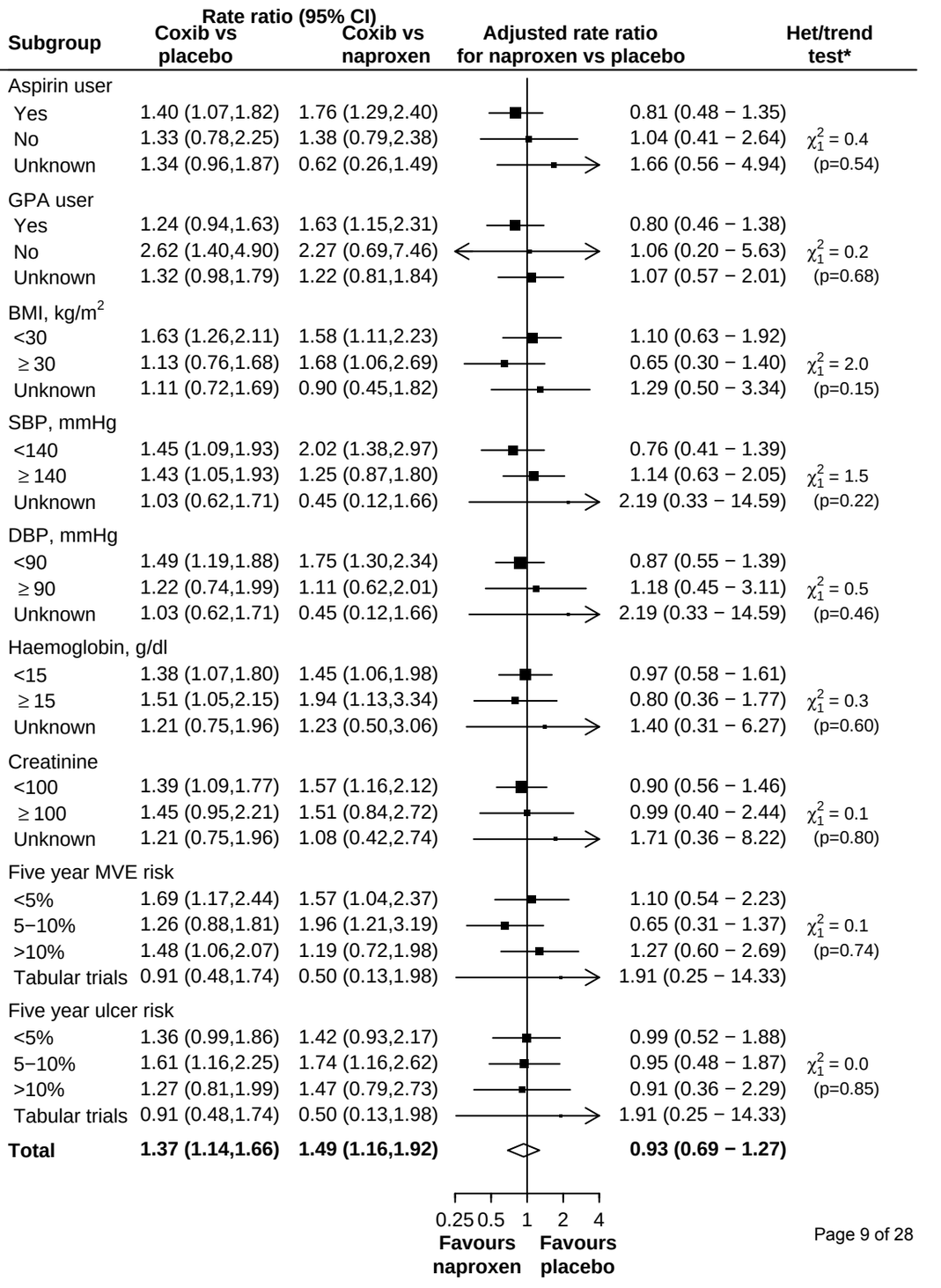




* Tests for trend (or heterogeneity) exclude the 'unknown' categories

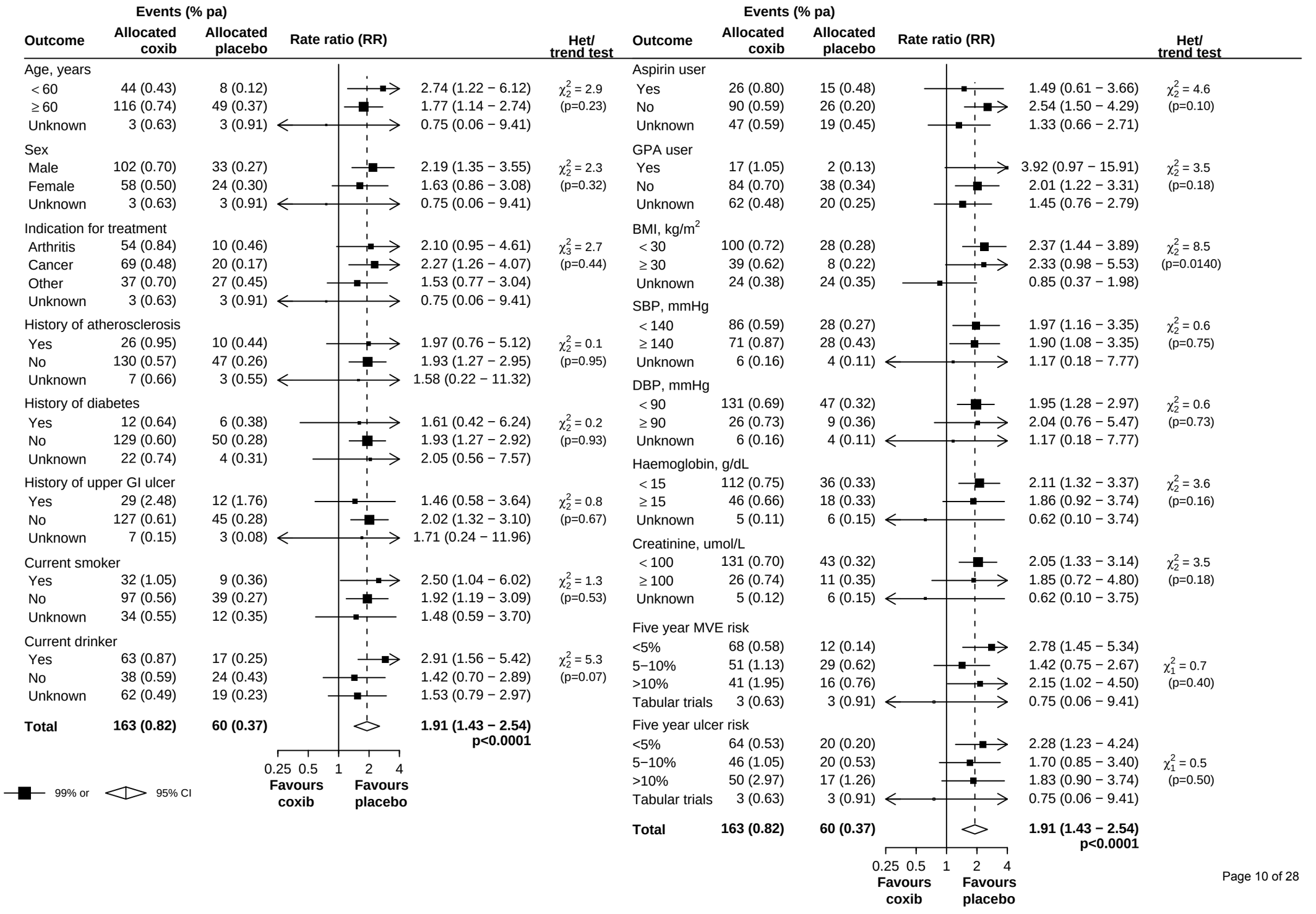
Webfigure 6: Effect of naproxen on major vascular events, by baseline characteristics



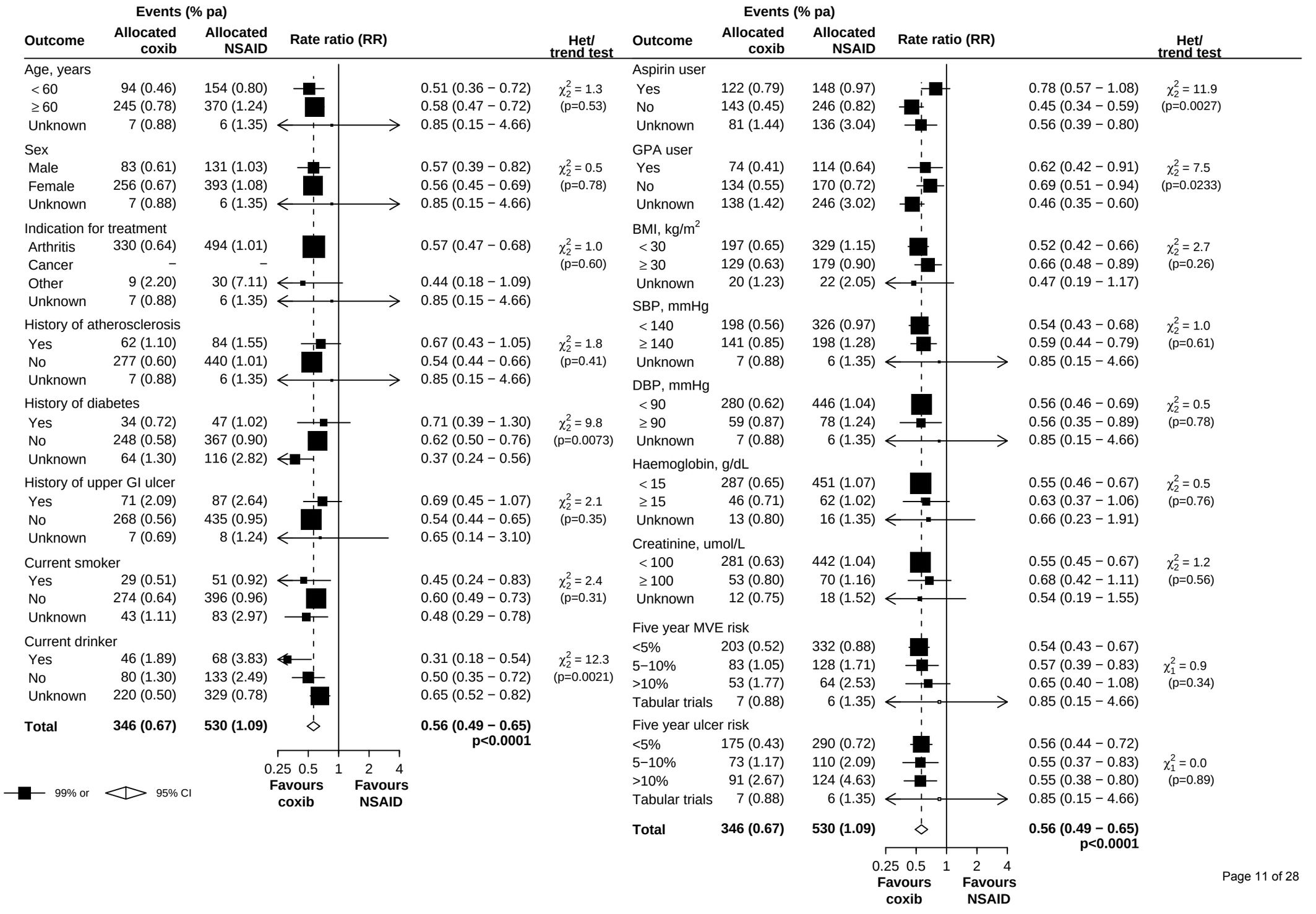


* Tests for trend (or heterogeneity) exclude the 'unknown' categories

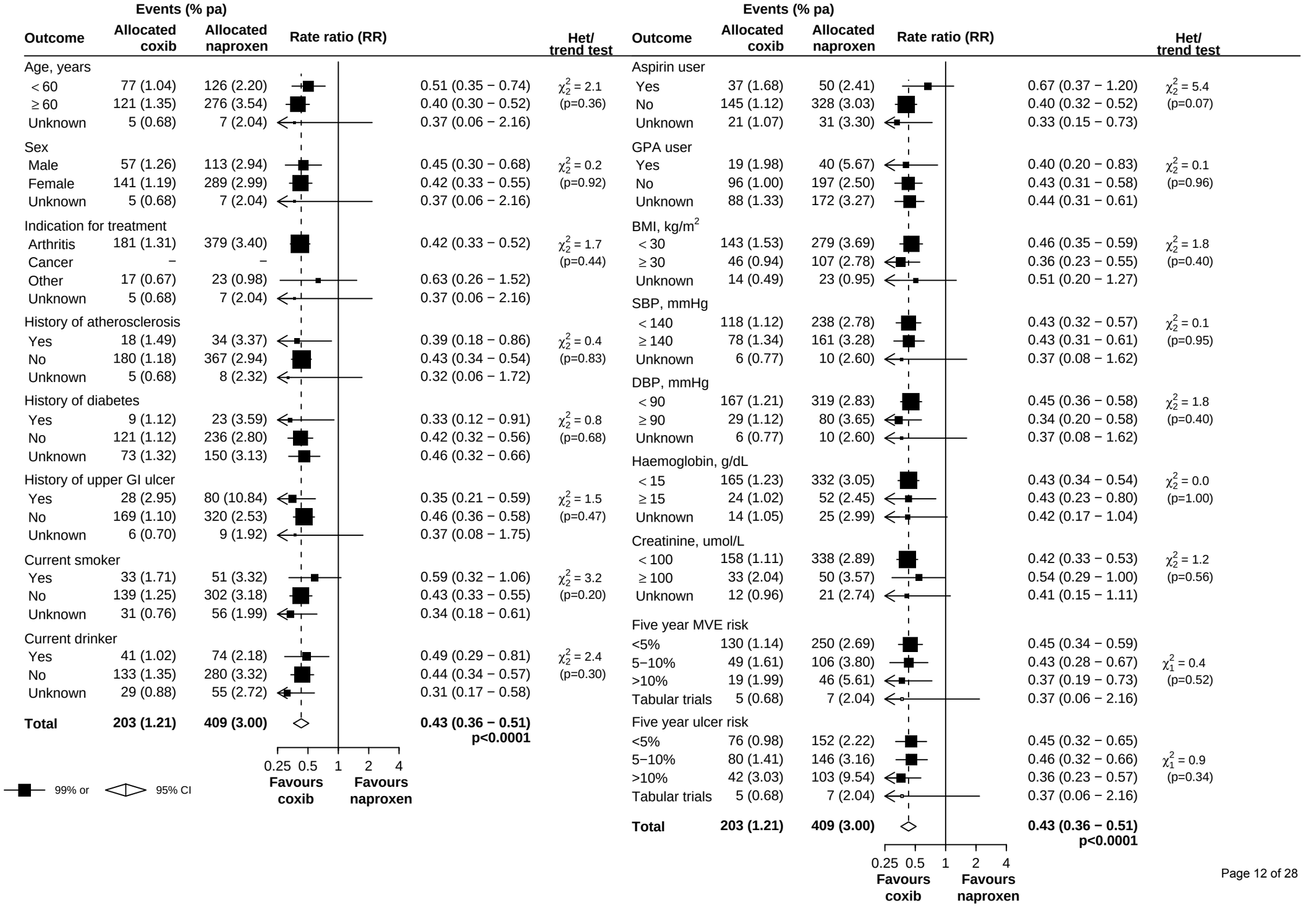
Webfigure 7: Effect of coxib therapy on any symptomatic upper GI event, by baseline characteristics



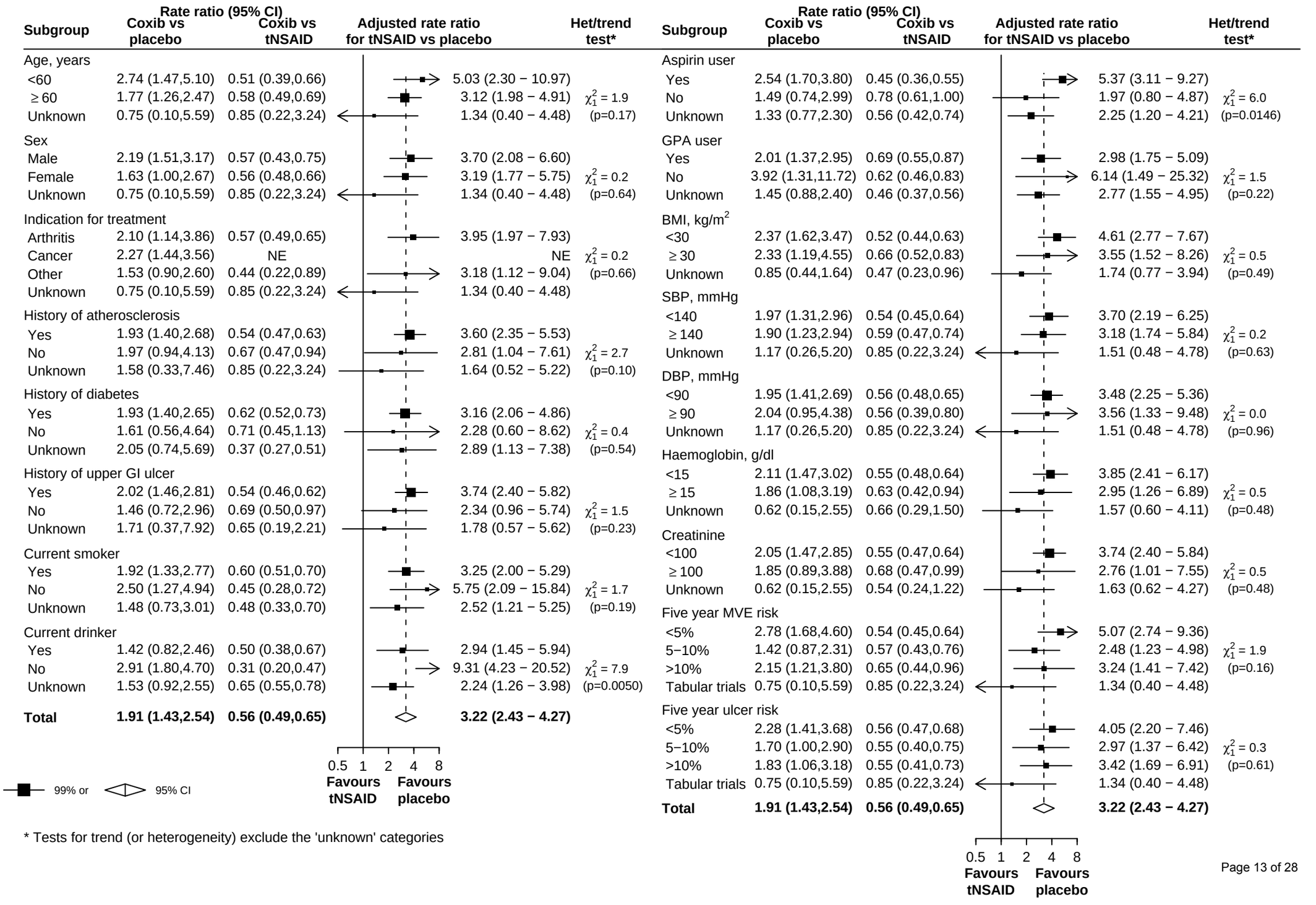
Webfigure 8: Comparisons of coxibs vs non−naproxen NSAIDs. Effect on any symptomatic upper GI event by baseline characteristics



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

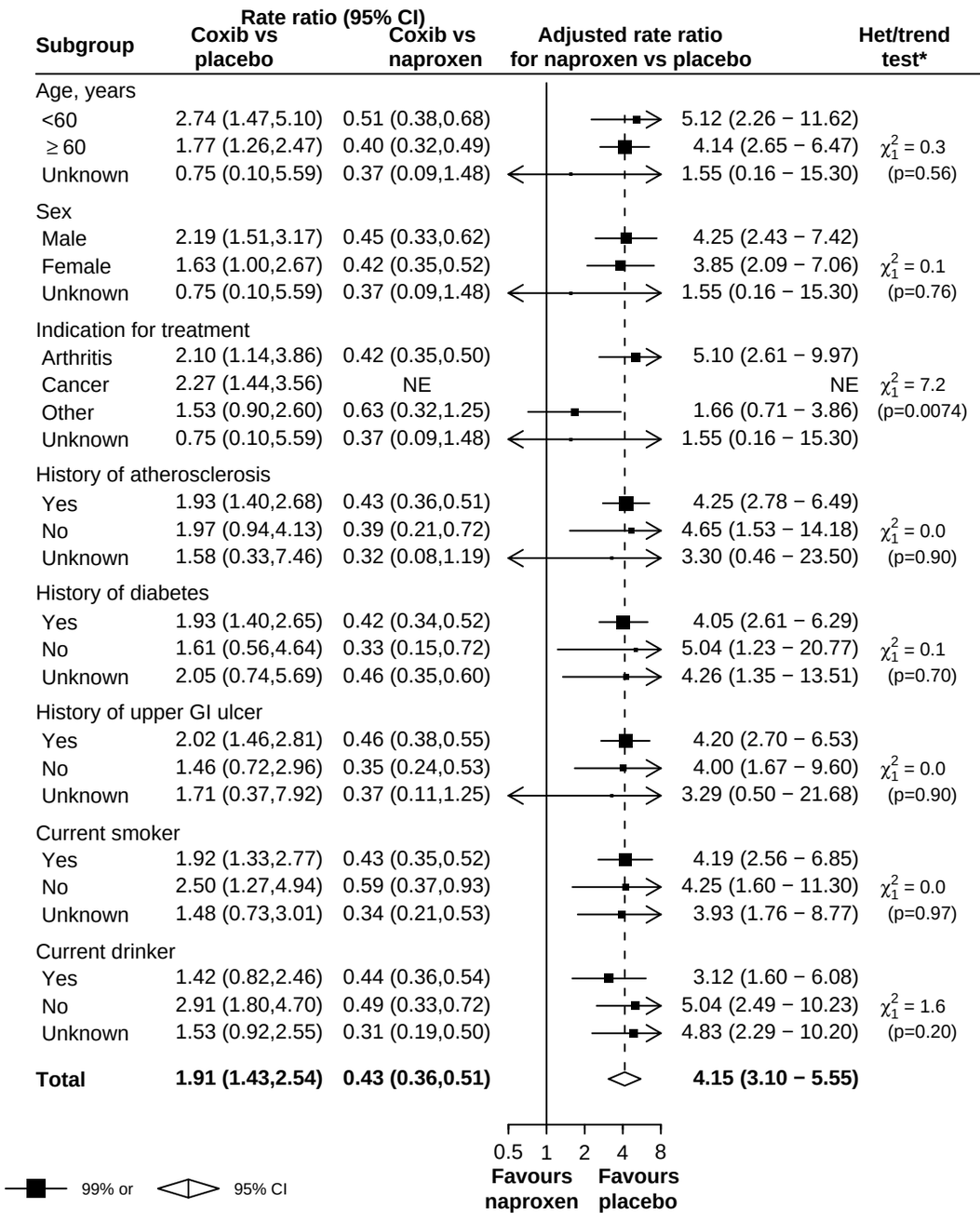


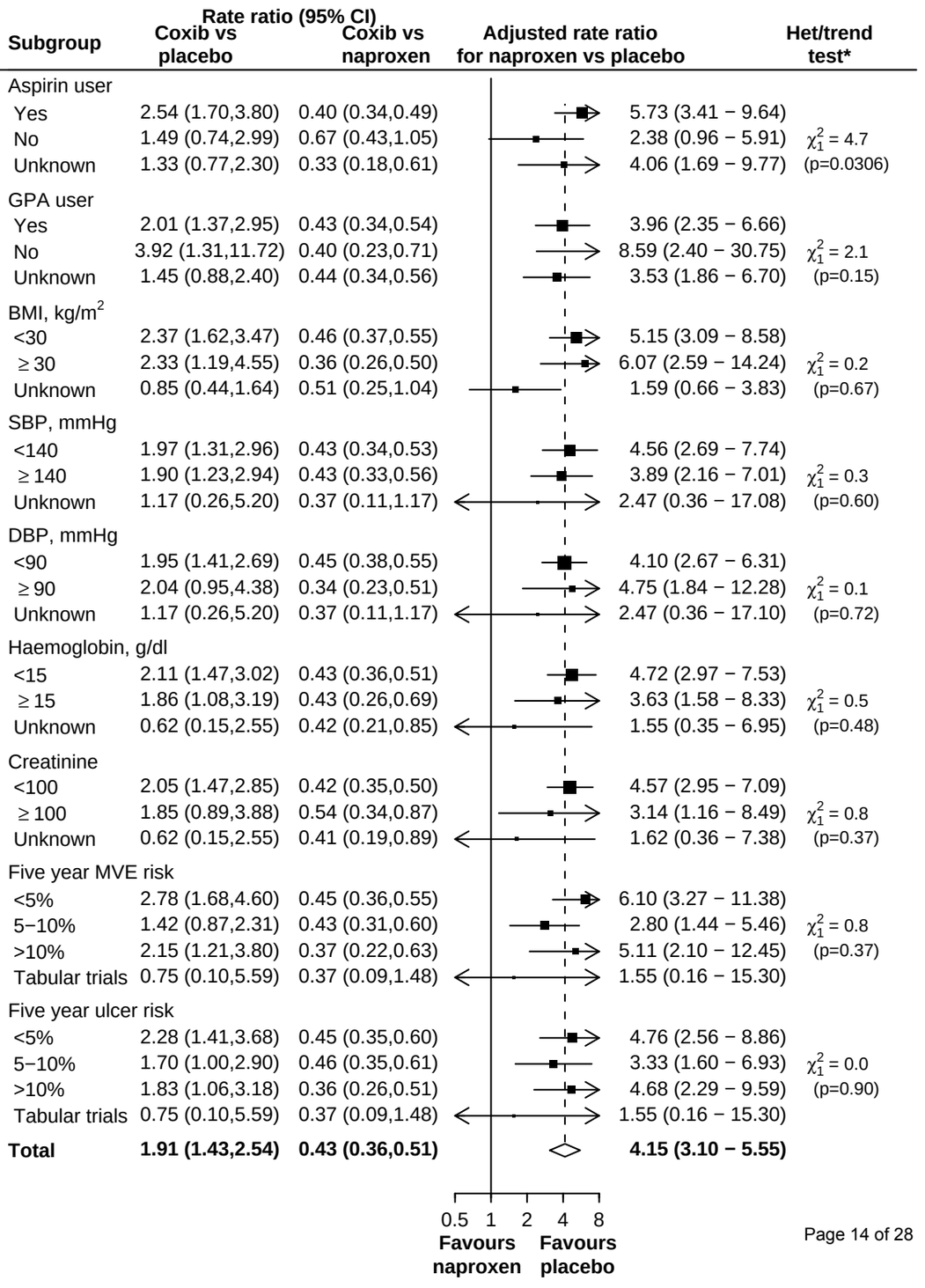
Webfigure 10: Effect of non−naproxen tNSAIDs on any symptomatic upper GI event, by baseline characteristics



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

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

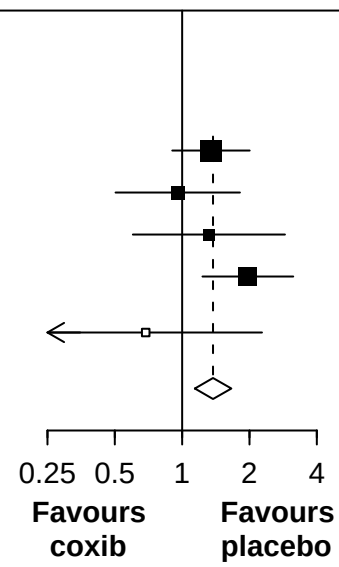




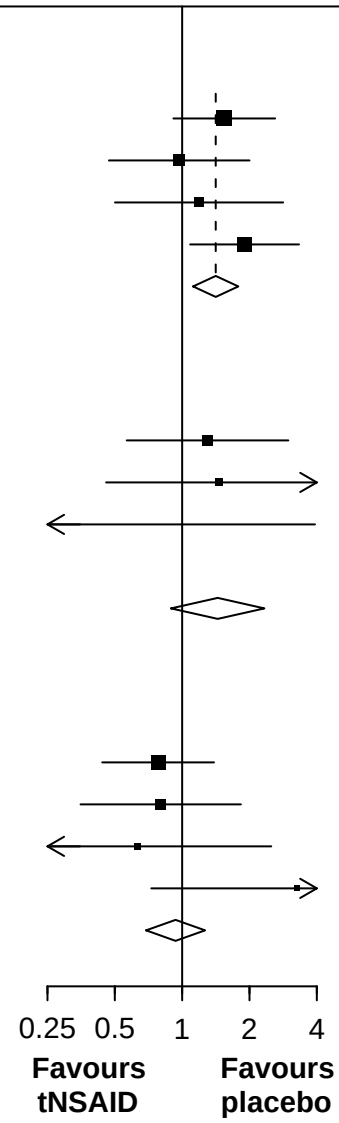
* Tests for trend (or heterogeneity) exclude the 'unknown' categories

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

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**	80	139 (1.27)	64 (0.99)	1.35 (0.90 − 2.00)	
6−12 months	13	38 (1.08)	35 (1.09)	0.96 (0.50 − 1.81)	χ^2_1=2.9
12−18 months	8	30 (1.11)	20 (0.80)	1.32 (0.60 − 2.88)	(p=0.09)
>18 months	7	91 (1.15)	43 (0.57)	1.97 (1.23 − 3.14)	
Unknown	6	9 (0.57)	13 (0.82)		
Total	**86**	**307 (1.15)**	**175 (0.82)**	**1.37 (1.14 − 1.66) p=0.0009**	



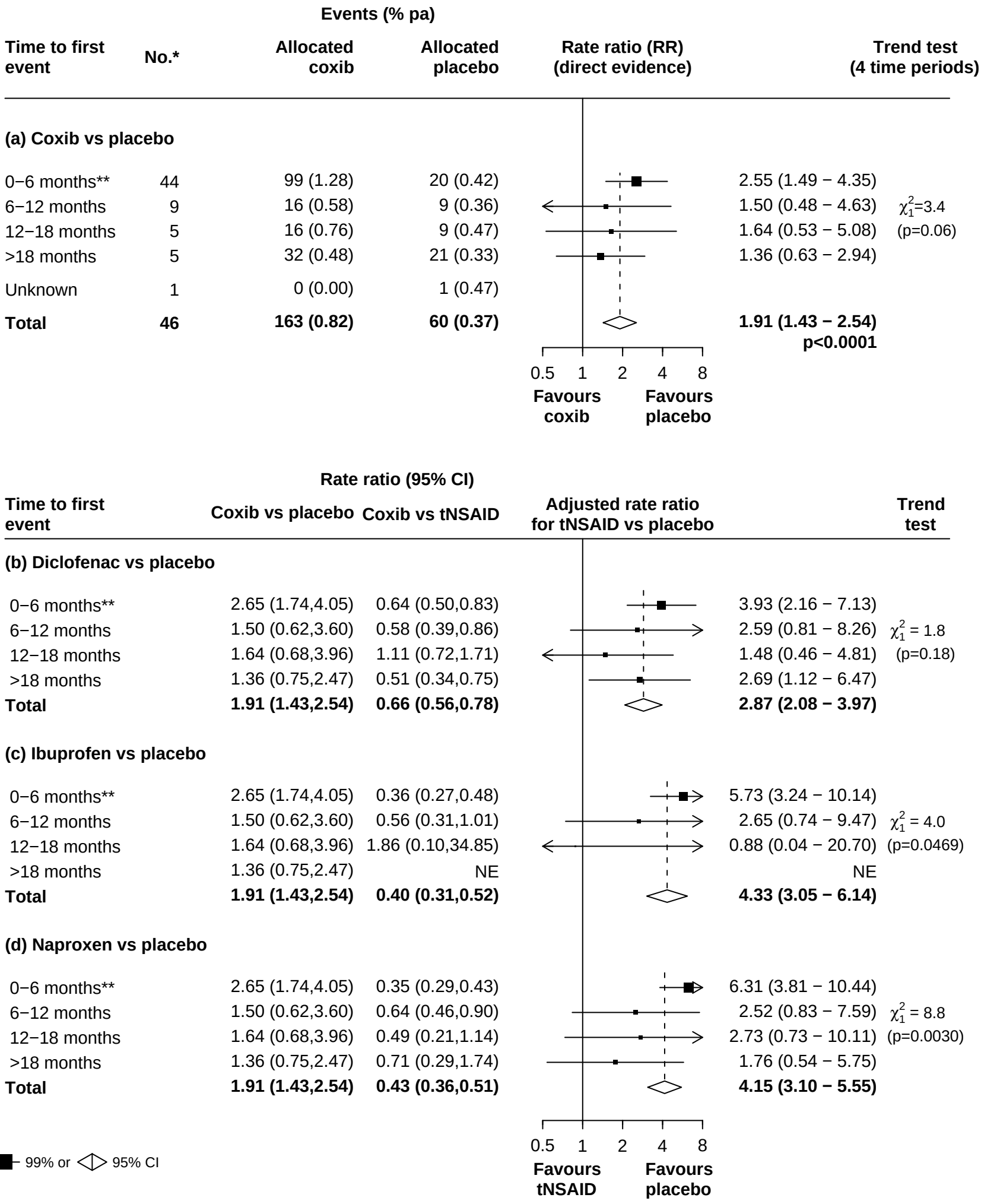
Time to first event	Rate ratio (95% CI) Coxib vs placebo	Coxib vs tNSAID	Adjusted rate ratio for tNSAID vs placebo	Trend test
(b) Diclofenac vs placebo				
0−6 months**	1.36 (0.98,1.89)	0.89 (0.67,1.18)	1.54 (0.91 − 2.60)	
6−12 months	0.96 (0.58,1.57)	0.98 (0.73,1.34)	0.97 (0.47 − 2.00)	χ^2_1 = 0.6
12−18 months	1.32 (0.72,2.41)	1.11 (0.78,1.58)	1.19 (0.50 − 2.83)	(p=0.44)
>18 months	1.97 (1.37,2.82)	1.03 (0.80,1.34)	1.90 (1.09 − 3.33)	
Total	**1.37 (1.14,1.66)**	**0.97 (0.84,1.12)**	**1.41 (1.12 − 1.78)**	
(c) Ibuprofen vs placebo				
0−6 months**	1.36 (0.98,1.89)	0.97 (0.53,1.78)	1.30 (0.57 − 2.98)	
6−12 months	0.96 (0.58,1.57)	0.65 (0.28,1.49)	1.47 (0.46 − 4.70)	χ^2_1 = 0.7
12−18 months	1.32 (0.72,2.41)	7.20 (0.38,134.88)	0.18 (0.01 − 3.92)	(p=0.41)
>18 months	1.97 (1.37,2.82)	NE	NE	
Total	**1.37 (1.14,1.66)**	**0.92 (0.58,1.46)**	**1.44 (0.89 − 2.33)**	
(d) Naproxen vs placebo				
0−6 months**	1.36 (0.98,1.89)	1.89 (1.33,2.69)	0.78 (0.44 − 1.39)	
6−12 months	0.96 (0.58,1.57)	1.27 (0.79,2.05)	0.80 (0.35 − 1.83)	χ^2_1 = 2.4
12−18 months	1.32 (0.72,2.41)	1.84 (0.59,5.75)	0.63 (0.16 − 2.50)	(p=0.12)
>18 months	1.97 (1.37,2.82)	0.74 (0.25,2.18)	3.25 (0.73 − 14.47)	
Total	**1.37 (1.14,1.66)**	**1.49 (1.16,1.92)**	**0.93 (0.69 − 1.27)**	



99% or 95% CI

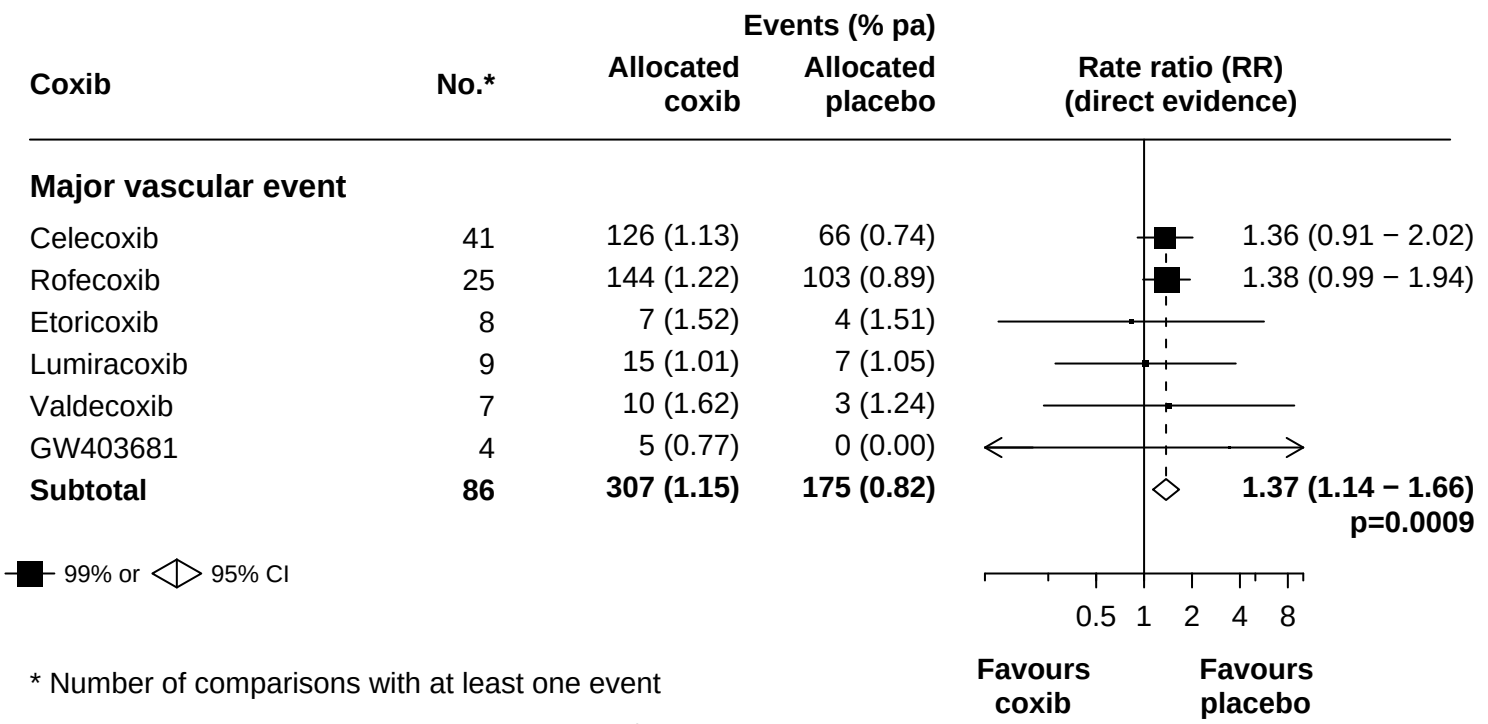
* Number of comparisons with at least one event in that period
** Includes tabular data from trials known to be <6 months duration. Other tabular trials for which events dates are unknown only contribute to the summary diamond.

Webfigure 13: Effect of coxibs, non−naproxen tNSAIDs and naproxen on any symptomatic upper GI event, 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 14: Effect of coxib therapy on major vascular events, by type of coxib

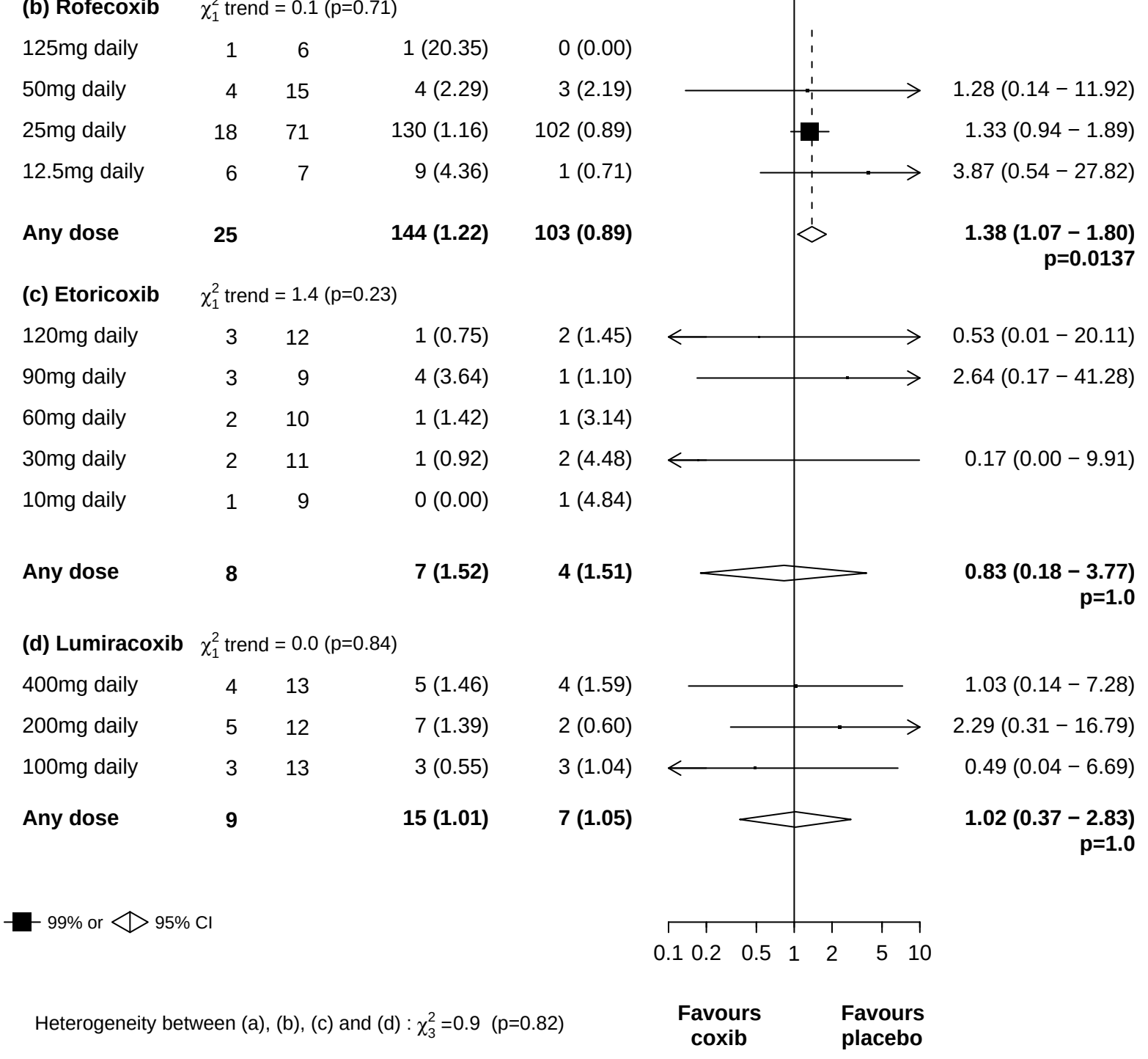


* Number of comparisons with at least one event

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**

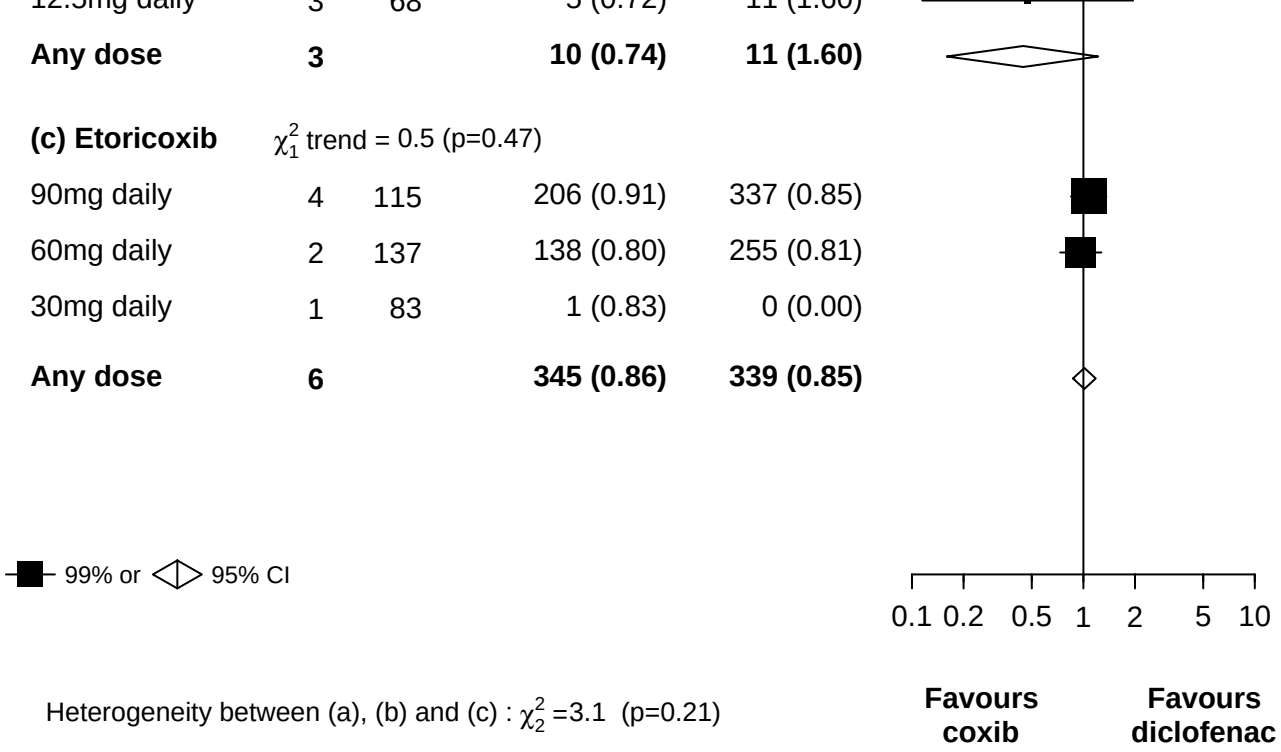


Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =0.9 (p=0.82)

* 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**

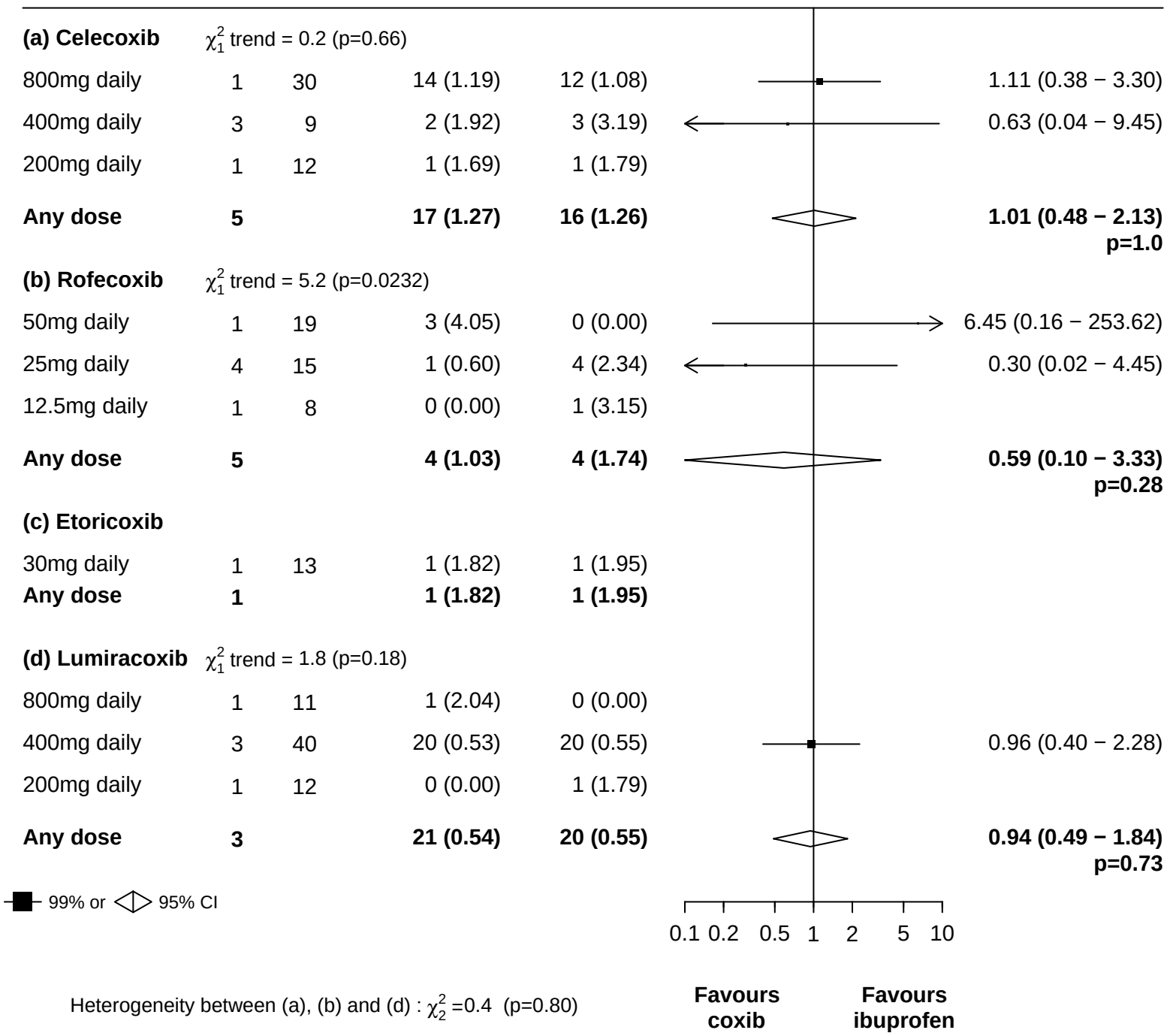


Heterogeneity between (a), (b) and (c) : χ^2_2 =3.1 (p=0.21)

* 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**

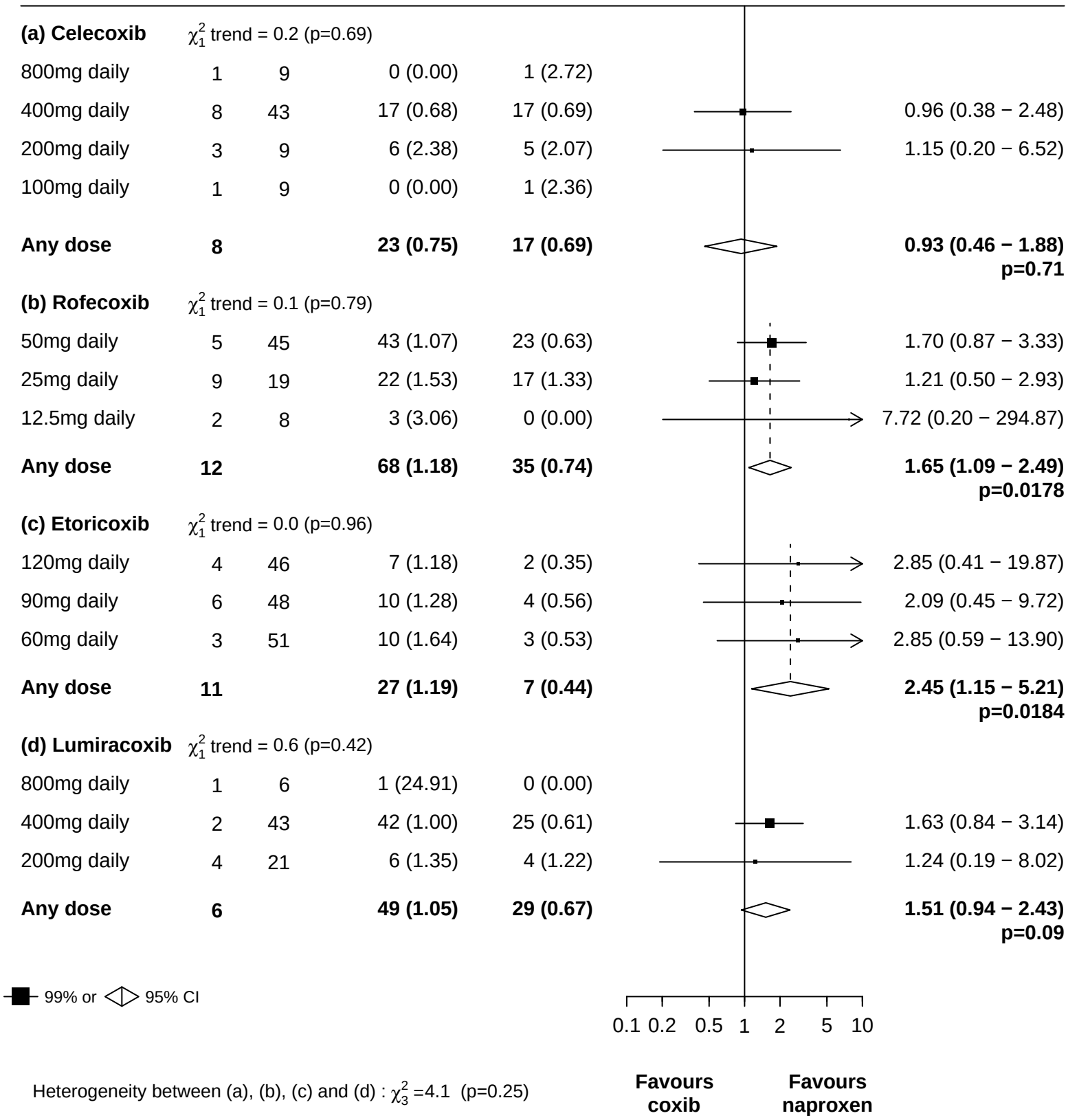


Heterogeneity between (a), (b) and (d) : χ^2_2 =0.4 (p=0.80)

* 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

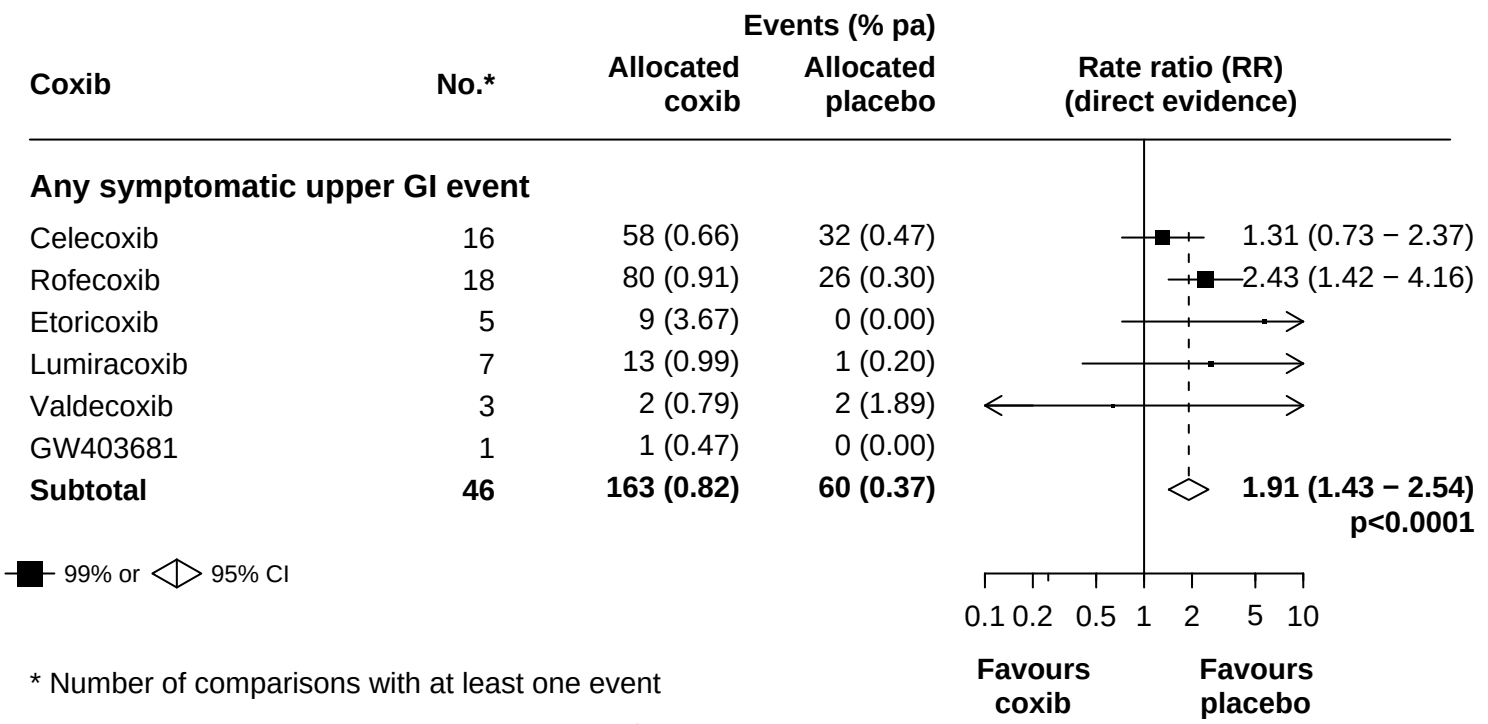
Dose	No.*	Mean FU (weeks)	Events (% pa) Allocated coxib	Events (% pa) Allocated naproxen	Rate ratio (RR) (direct evidence)
(a) Celecoxib	χ^2_1 trend = 0.2 (p=0.69)				
800mg daily	1	9	0 (0.00)	1 (2.72)	
400mg daily	8	43	17 (0.68)	17 (0.69)	0.96 (0.38 − 2.48)
200mg daily	3	9	6 (2.38)	5 (2.07)	1.15 (0.20 − 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

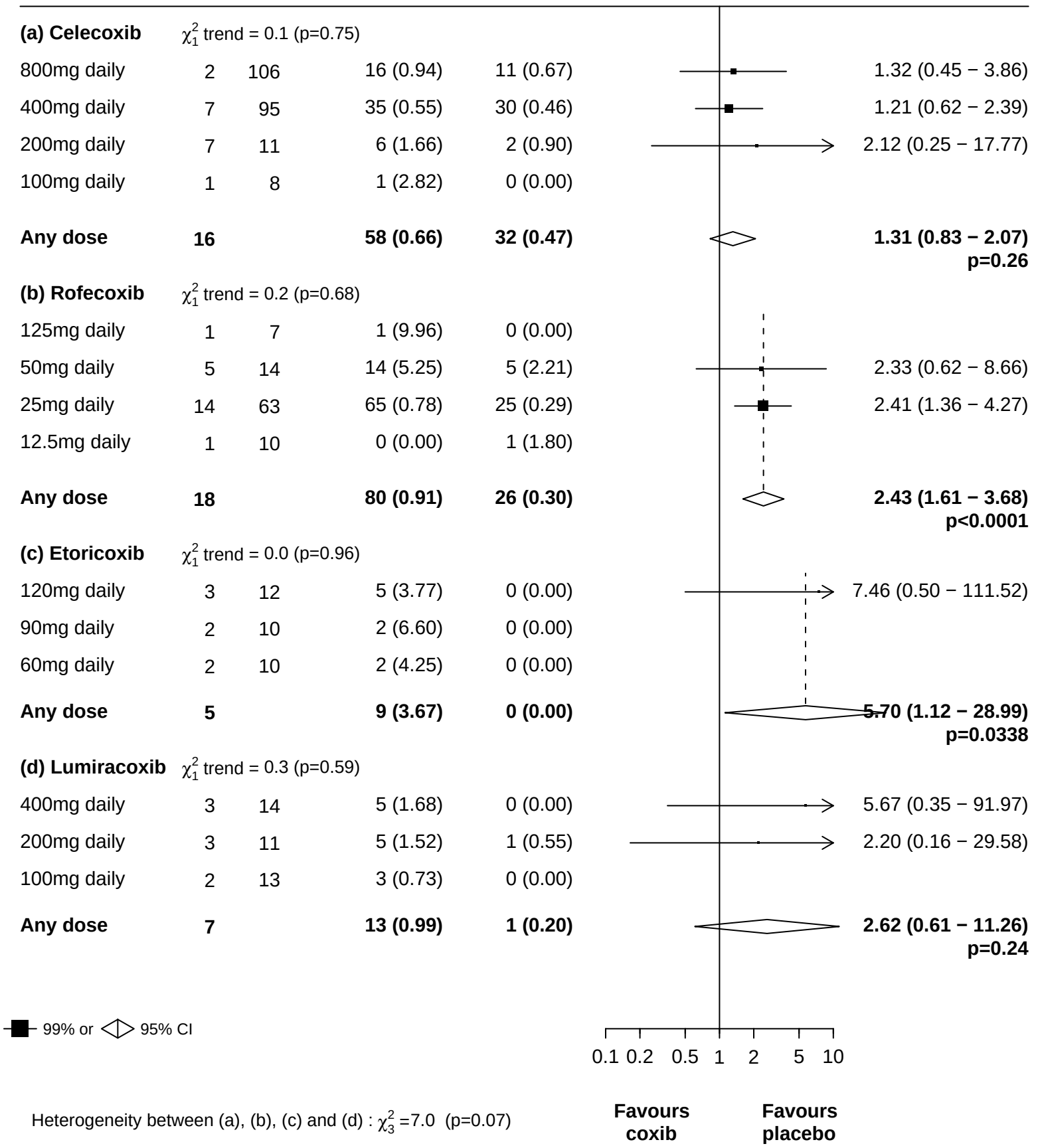


* Number of comparisons with at least one event

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**

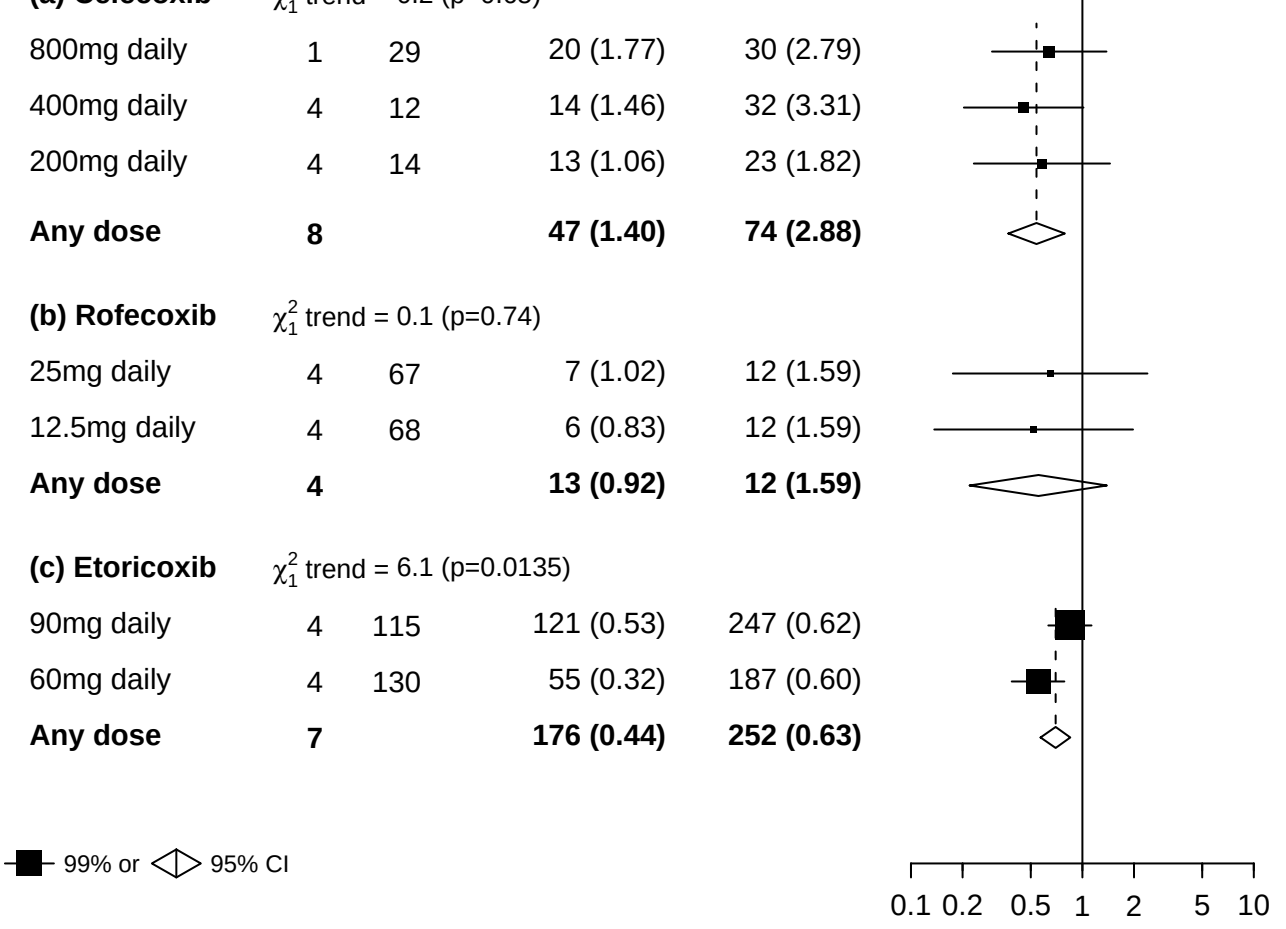


Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =7.0 (p=0.07)

* 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**

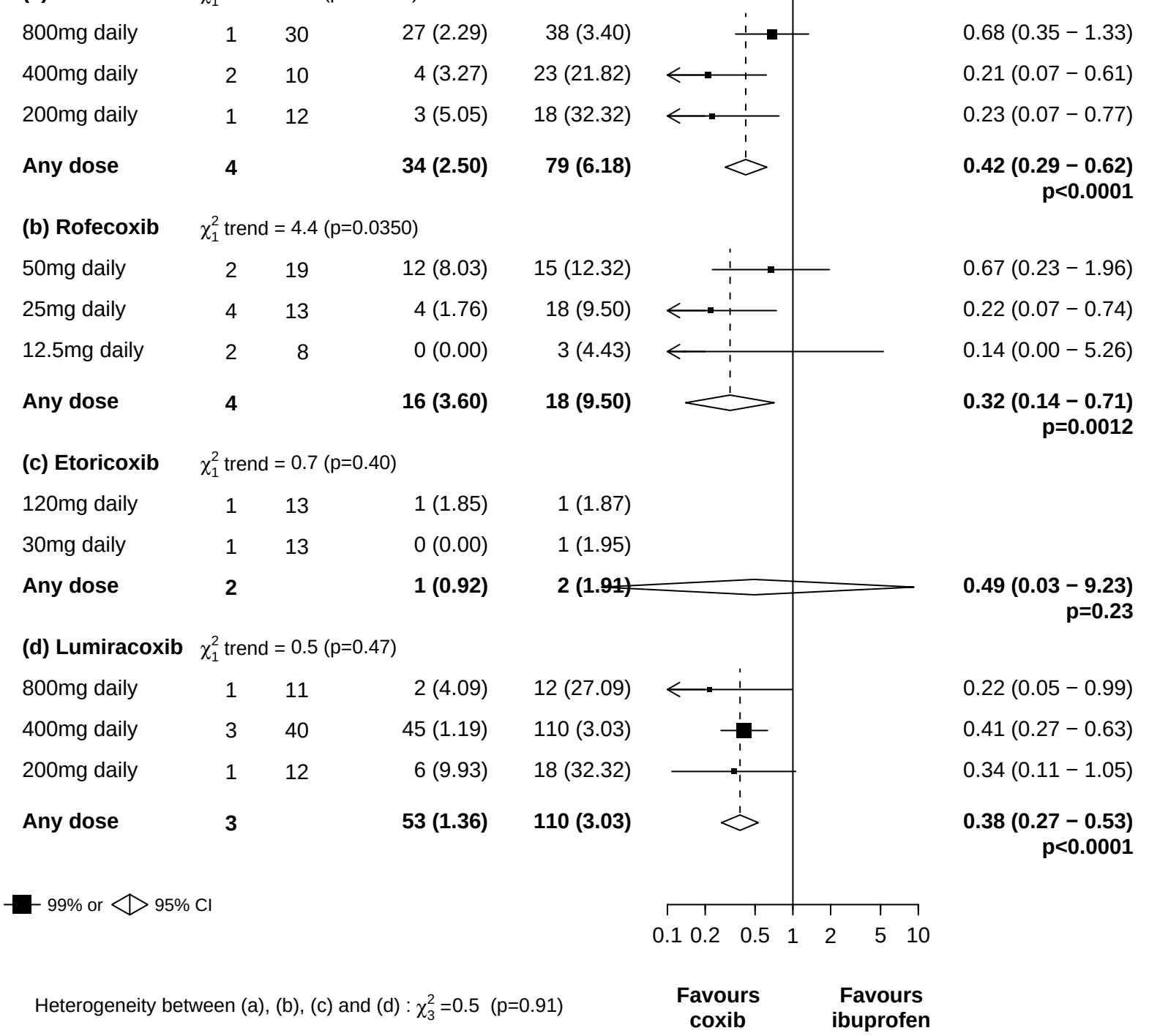


Heterogeneity between (a), (b) and (c) : χ^2_2 =1.7 (p=0.43)

* 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**

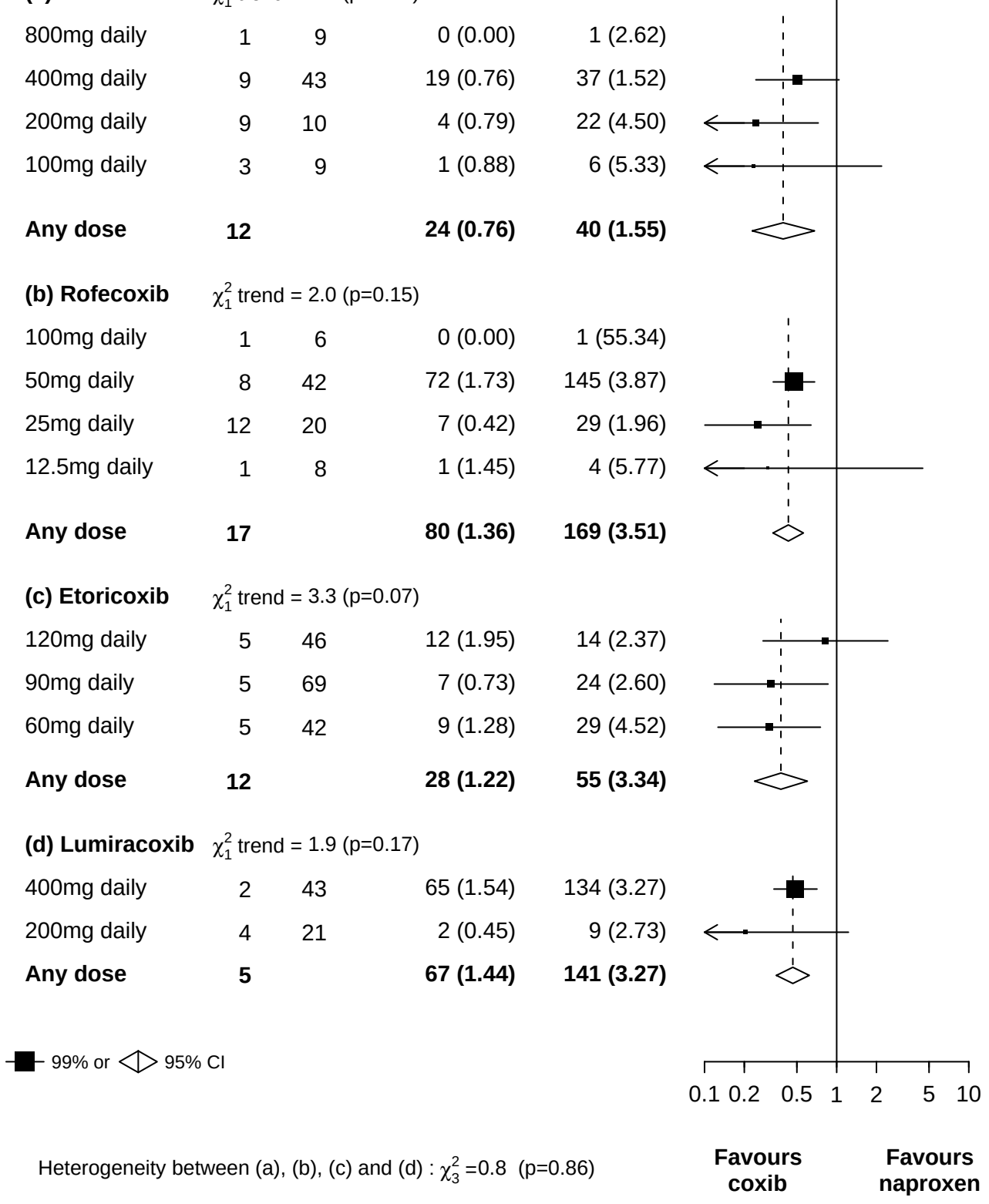


Heterogeneity between (a), (b), (c) and (d) : χ^2_3 =0.5 (p=0.91)

* 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.