Web appendix 2: Additional results

Content

External adjudication of events per outcome

Table 1: External adjudication of events

Trial	Myocardial infarction	Stroke	Cardiovascular death	APTC outcome
ADAPT	Yes	Yes	Yes	Yes
Aisen 2003	No	No	No	Yes
Geusens 2004	No	No	No	Yes
APC	Yes	Yes	Yes	Yes
GAIT	No	No	No	Yes
IQ5-97-02-001	No	No	No	Yes
PreSAP	Yes	Yes	Yes	Yes
Lehmann 2005	Yes	Yes	Yes	Yes
APPROVe	Yes	Yes	Yes	Yes
Reines 2004	Yes	Yes	Yes	Yes
Thal 2005	Yes	Yes	Yes	Yes
VICTOR	Yes	Yes	Yes	Yes
ViP	Yes	Yes	Yes	Yes
A3191152	No	No	No	Yes
SUCCESS-1 (USA/Canada)	No	No	No	Yes
ADVANTAGE	Yes	Yes	Yes	Yes
VIGOR	Yes	Yes	Yes	Yes
TARGET (0117)	Yes	Yes	Yes	Yes
CLASS (N49-98-02-035)	No	No	No	Yes
TARGET (2332)	Yes	Yes	Yes	Yes
CAESAR	No	No	No	Yes
CLASS (N49-98-02-102)	No	No	No	Yes
Emery 1999	No	No	No	Yes
SUCCESS-1 (World)	No	No	No	Yes
EDGE	Yes	Yes	Yes	Yes
EDGE II	Yes	Yes	Yes	Yes
MEDAL	Yes	Yes	Yes	Yes
Cannon 2000	No	No	No	Yes
Saag 2000	No	No	No	Yes
Fleischmann 2003	No	No	No	Yes
Tannenbaum 2004	No	No	No	Yes

APTC, Antiplatelet Trialist Collaboration; SAE, serious adverse event; SND, standard normal distribution
Death from any cause not considered (no external adjudication required)

Model fit

Table 2 presents the assessment of model fit. Criteria for an adequate fit of the model were all satisfied for all outcomes.

Table 2: Assessment of model fit

Outcome	Data points	Residual deviance	Residuals	Q-Q plots
		Mean	Number (%)	

			within 1.96 SND	
Myocardial infarction	62	66	61 (98%)	Adequate
Stroke	56	52	56 (100%)	Adequate
Cardiovascular death	56	56	55 (98%)	Adequate
Death from any cause	56	54	55 (98%)	Adequate
APTC outcome	60	63	60 (100%)	Adequate

APTC, Antiplatelet Trialist Collaboration; SAE, serious adverse event; SND, standard normal distribution
The following grades for the Q-Q plot assessment were used: adequate, inadequate

Between trial heterogeneity τ^2

Table 3 presents estimates of the between trial variance (τ^2) as measure of statistical heterogeneity between trials for the model assuming one common variance estimate τ^2 for all comparisons. All τ^2 estimates indicated low heterogeneity except for the outcome myocardial infarction where the τ^2 estimate indicated moderate heterogeneity. We therefore considered treatment effects from direct comparisons as homogeneous. However, given the wide 95% credibility intervals, relevant heterogeneity can not be excluded. In the sensitivity analysis, estimated τ^2 were in general also low to moderate except for selected comparisons in the analysis on myocardial infarction. However, 95% credibility intervals were wide. Results of analyses employing a model assuming one common distribution for the different treatment effects separately are presented below (p. 2). In summary, between trial heterogeneity was considered adequate for all outcomes.

Table 3: Estimates of between trial heterogeneity

	τ^2 (95%-CI)
Myocardial infarction	0.12 (0.00-0.79)
Stroke	0.07 (0.00-0.53)
Cardiovascular death	0.09 (0.00-0.82)
Death from any cause	0.03 (0.00-0.27)
APTC outcome	0.04 (0.00-0.29)

Presented is the between-trial variance τ^2 as a measure of the heterogeneity between trials in the network for each outcome and comparison. A τ^2 estimate of 0.04 may be interpreted as a low, 0.14 as a moderate and 0.40 as a substantial degree of heterogeneity between trials. Note that we used a common τ^2 estimate for all comparisons for all analyses.
APTC, Antiplatelet Trialist Collaboration

Inconsistency

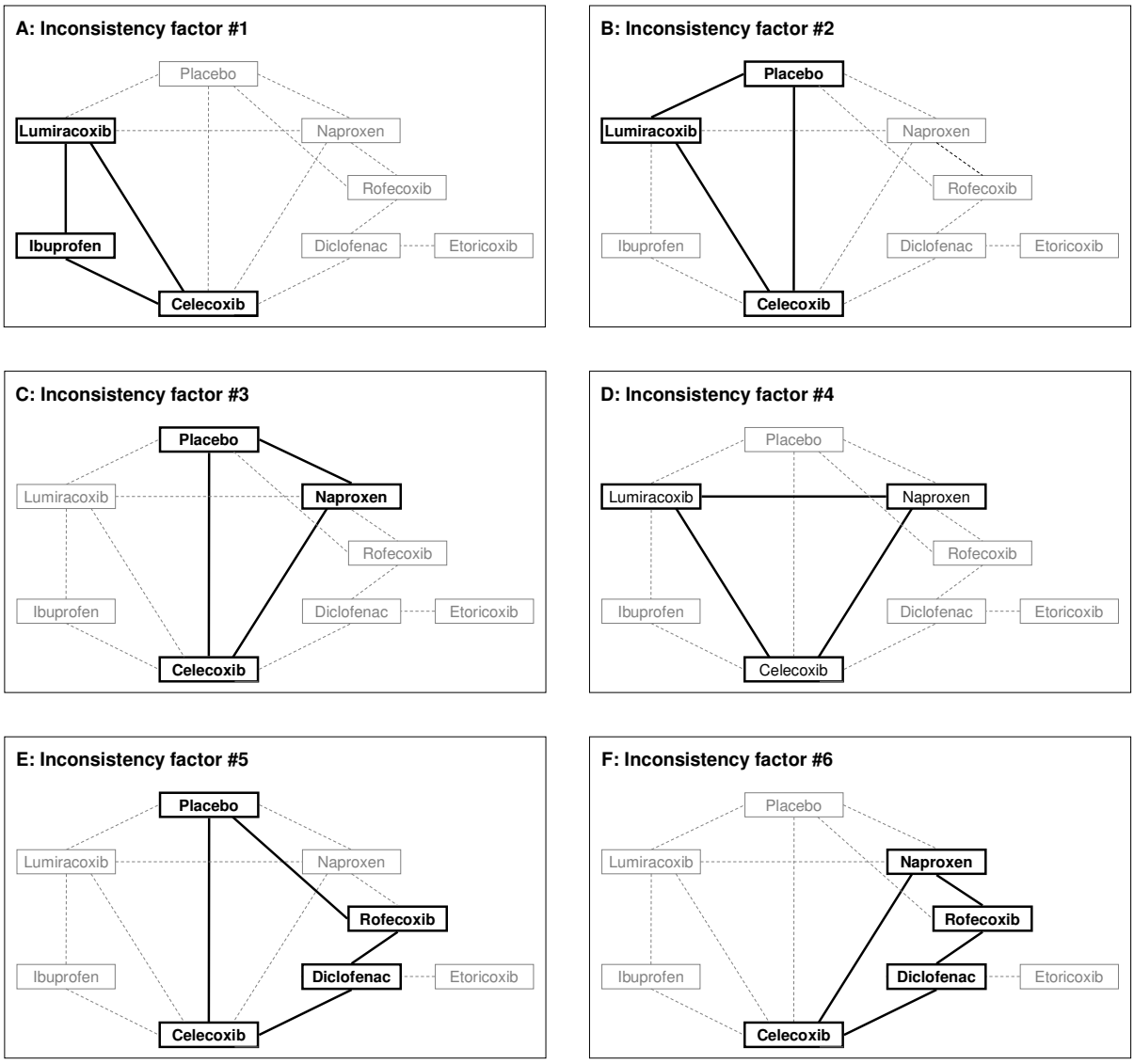
Table 4 presents estimated inconsistencies with 95% credibility intervals and Figure 1 presents corresponding loop to each inconsistency factor. None of the loops showed inconsistency above 50%. We therefore considered the network to be consistent for all outcomes. However, 95% credibility intervals were wide and potential inconsistency can not be excluded.

Table 4: Assessment of inconsistency

Outcome	ICF #1 (95%-CI)	ICF #2 (95%-CI)	ICF #3 (95%-CI)	ICF #4 (95%-CI)	ICF #5 (95%-CI)	ICF #6 (95%-CI)
Myocardial infarction	5% (0-144%)	0% (0-293%)	16% (0-276%)	7% (0-135%)	4% (0-201%)	29% (0-257%)
Stroke	0% (0-210%)	3% (0-285%)	1% (0-127%)	3% (0-116%)	1% (0-252%)	3% (0-257%)
Cardiovascular death	3% (0-248%)	28% (0-1409%)	2% (0-390%)	11% (0-194%)	11% (0-545%)	13% (0-867%)
Death from any cause	12% (0-253%)	45% (0-3075%)	23% (0-1101%)	23% (0-203%)	110% (0-1522%)	35% (0-1217%)
APTC outcome	9% (0-72%)	11% (0-310%)	3% (0-122%)	5% (0-102%)	3% (0-125%)	33% (0-447%)

APTC, Antiplatelet Trialist Collaboration

Figure 1: Inconsistency factors and corresponding loops



Each panel presents corresponding loops to the six inconsistency factors. Corresponding loops are highlighted in bold e.g. inconsistency factor #1 corresponds to the loop consisting of ibuprofen, celecoxib, and lumiracoxib.

Association between outcomes and Cox-2 selectivity

We found little evidence for an association between the risk for any of the outcomes and Cox-2 selectivity:

Table 5: Association between outcomes and Cox-2 selectivity

Outcome	Regression coefficient (95%-CI)
Myocardial infarction	-0.10 (-0.27 to 0.05)
Stroke	0.02 (-0.11 to 0.17)
Cardiovascular death	-0.05 (-0.22 to 0.09)
Death from any cause	-0.04 (-0.15 to 0.06)
APTC outcome	-0.02 (-0.11 to 0.07)

APTC, Antiplatelet Trialist Collaboration

Interpretation of regression coefficient: difference in log rate ratio (comparison to placebo) for each unit increase in cox-2 selectivity as measured by the log(IC_{80} ratio)

Additional analyses

Influence of methodological characteristics of trials

Table 6 presents results of sensitivity analyses to explore the influence of methodological characteristics of trials. Sensitivity analyses supported the robustness of the results of the main analyses. However, given the low number of events, credibility intervals were very wide and sometimes, we were even not able to estimate the point estimate. Between trial heterogeneity was low to moderate for most analyses (median τ^2 0.10; range 0.02-0.25).

Table 6: Results of sensitivity analyses of methodological characteristics

	Main analysis	**Trials with external adjudication of events**	**Trials in patients with musculoskeletal diseases**	**Trials allowing the use of low-dose aspirin**
Myocardial infarction				
Patient-years	*117,218*	*105,141*	*83,068*	*110,541*
Accumulated events	*532*	*461*	*369*	*495*
Naproxen vs. Placebo	0.82 (0.37-1.67)	0.83 (0.27-2.09)	0.30 (0.01-14.72)	1.10 (0.44-2.34)
Ibuprofen vs. Placebo	1.61 (0.50-5.77)	1.45 (0.10-14.8)	0.83 (0.03-37.5)	1.84 (0.57-6.26)
Diclofenac vs. Placebo	0.82 (0.29-2.20)	1.05 (0.00-∞)	0.41 (0.01-22.6)	0.75 (0.22-2.34)
Celecoxib vs. Placebo	1.35 (0.71-2.72)	1.22 (0.48-3.01)	0.69 (0.03-33.3)	1.40 (0.71-2.92)
Etoricoxib vs. Placebo	0.75 (0.23-2.39)	0.95 (0.00-∞)	0.38 (0.01-22.7)	0.69 (0.18-2.51)
Rofecoxib vs. Placebo	2.12 (1.26-3.56)	2.30 (1.13-4.62)	1.20 (0.04-63.6)	2.51 (1.43-4.84)
Lumiracoxib vs. Placebo	2.00 (0.71-6.21)	1.41 (0.20-6.63)	0.95 (0.05-43. 3)	2.41 (0.83-7.44)
Stroke				
Patient-years	*115,770*	*105,141*	*82,166*	*109,897*
Accumulated events	*367*	*304*	*239*	*338*
Naproxen vs. Placebo	1.76 (0.91-3.33)	1.54 (0.67-4.04)	1.04 (0.07-20.6)	2.16 (1.09-4.44)
Ibuprofen vs. Placebo	3.36 (1.00-11.6)	2.48 (0.38-22.4)	2.12 (0.15-55.3)	3.64 (1.20-13.0)
Diclofenac vs. Placebo	2.86 (1.09-8.36)	0.80 (0.00-∞)	1.60 (0.08-53.6)	2.76 (0.89-8.28)
Celecoxib vs. Placebo	1.12 (0.60-2.06)	1.08 (0.48-2.46)	0.60 (0.03-15.9)	1.13 (0.62-2.02)
Etoricoxib vs. Placebo	2.67 (0.82-8.72)	0.71 (0.00-∞)	1.43 (0.06-52.3)	2.56 (0.74-8.56)
Rofecoxib vs. Placebo	1.07 (0.60-1.82)	0.86 (0.43-1.61)	0.65 (0.03-14.8)	0.97 (0.53-1.63)
Lumiracoxib vs. Placebo	2.81 (1.05-7.48)	2.18 (0.61-11.0)	1.80 (0.20-37.6)	3.18 (1.31-8.31)
Cardiovascular death				
Patient-years	*115,773*	*105,144*	*82,170*	*109,900*

Table 6: Results of sensitivity analyses of methodological characteristics

	Main analysis	Trials with external adjudication of events	Trials in patients with musculoskeletal diseases	Trials allowing the use of low-dose aspirin
Accumulated events	*294*	*233*	*205*	*266*
Naproxen vs. Placebo	0.98 (0.41-2.37)	1.15 (0.37-3.28)	n/e	0.90 (0.29-2.39)
Ibuprofen vs. Placebo	2.39 (0.69-8.64)	2.66 (0.30-25.3)	n/e	2.05 (0.54-7.90)
Diclofenac vs. Placebo	3.98 (1.48-12.7)	1.40 (0.00-∞)	n/e	2.63 (0.80-9.54)
Celecoxib vs. Placebo	2.07 (0.98-4.55)	1.63 (0.61-4.56)	n/e	1.70 (0.79-3.89)
Etoricoxib vs. Placebo	4.07 (1.23-15.7)	1.42 (0.00-∞)	n/e	2.69 (0.67-11.7)
Rofecoxib vs. Placebo	1.58 (0.88-2.84)	1.92 (0.91-4.02)	n/e	2.15 (1.00-4.54)
Lumiracoxib vs. Placebo	1.89 (0.64-7.09)	2.02 (0.39-12.1)	n/e	1.77 (0.49-6.37)
Death from any cause				
Patient-years	*114,118*	*n/a*	*n/a*	*107,987*
Accumulated events	*654*	*n/a*	*n/a*	*587*
Naproxen vs. Placebo	1.23 (0.71-2.12)	n/e	n/e	1.28 (0.63-2.41)
Ibuprofen vs. Placebo	1.77 (0.73-4.30)	n/e	n/e	1.69 (0.67-4.18)
Diclofenac vs. Placebo	2.31 (1.00-4.95)	n/e	n/e	1.44 (0.67-3.46)
Celecoxib vs. Placebo	1.50 (0.96-2.54)	n/e	n/e	1.31 (0.79-2.18)
Etoricoxib vs. Placebo	2.29 (0.94-5.71)	n/e	n/e	1.42 (0.63-3.92)
Rofecoxib vs. Placebo	1.56 (1.04-2.23)	n/e	n/e	1.78 (1.12-2.68)
Lumiracoxib vs. Placebo	1.75 (0.78-4.17)	n/e	n/e	1.74 (0.74-3.99)
APTC outcome				
Patient-years	*116,334*	*105,141*	*82,731*	*110,204*
Accumulated events	*1056*	*898*	*726*	*976*
Naproxen vs. Placebo	1.22 (0.78-1.93)	1.14 (0.58-2.17)	0.93 (0.15-7.47)	1.57 (1.01-2.49)
Ibuprofen vs. Placebo	2.26 (1.11-4.89)	2.23 (0.49-10.2)	1.90 (0.32-162)	2.42 (1.26-5.15)
Diclofenac vs. Placebo	1.60 (0.85-2.99)	0.92 (0.00-∞)	1.36 (0.19-11.8)	1.52 (0.75-2.93)
Celecoxib vs. Placebo	1.43 (0.94-2.16)	1.29 (0.68-2.36)	1.28 (0.19-10.6)	1.45 (0.99-2.16)
Etoricoxib vs. Placebo	1.53 (0.74-3.17)	0.89 (0.00-∞)	1.32 (0.17-12.0)	1.46 (0.66-3.03)
Rofecoxib vs. Placebo	1.44 (1.00-1.99)	1.45 (0.86-2.28)	1.51 (0.20-14.0)	1.66 (1.18-2.40)
Lumiracoxib vs. Placebo	2.04 (1.13-4.24)	1.76 (0.61-5.25)	1.70 (0.32-12.7)	2.28 (1.34-4.51)

APTC, Antiplatelet Trialist Collaboration; ITT, intention-to-treat analysis; n/e, not estimable

Comparison of fixed-effect and random-effects analyses with single and multiple τ^2 considered in the model

The fixed effect analysis showed virtually the same results as the main analysis confirming the evaluation of inconsistency and between trial heterogeneity described above. Because the number of trials and events was too low, we were not able to implement a model allowing for different between trial heterogeneity parameters for each comparison.

Table 7: Results of sensitivity analyses using different analysis methods

	Main analysis	Fixed effect analysis
Myocardial infarction		
Naproxen vs. Placebo	0.82 (0.37-1.67)	0.91 (0.51-1.58)
Ibuprofen vs. Placebo	1.61 (0.50-5.77)	1.61 (0.66-4.07)
Diclofenac vs. Placebo	0.82 (0.29-2.20)	0.85 (0.36-1.88)
Celecoxib vs. Placebo	1.35 (0.71-2.72)	1.35 (0.83-2.21)
Etoricoxib vs. Placebo	0.75 (0.23-2.39)	0.77 (0.31-1.77)
Rofecoxib vs. Placebo	2.12 (1.26-3.56)	2.31 (1.56-3.51)
Lumiracoxib vs. Placebo	2.00 (0.71-6.21)	2.01 (0.88-4.94)
Stroke		
Naproxen vs. Placebo	1.76 (0.91-3.33)	1.59 (0.91-2.76)
Ibuprofen vs. Placebo	3.36 (1.00-11.6)	2.94 (1.06-8.71)
Diclofenac vs. Placebo	2.86 (1.09-8.36)	2.58 (0.99-6.75)
Celecoxib vs. Placebo	1.12 (0.60-2.06)	1.06 (0.62-1.80)
Etoricoxib vs. Placebo	2.67 (0.82-8.72)	2.52 (0.89-7.01)
Rofecoxib vs. Placebo	1.07 (0.60-1.82)	0.97 (0.62-1.51)
Lumiracoxib vs. Placebo	2.81 (1.05-7.48)	2.37 (1.08-5.33)
Cardiovascular death		
Naproxen vs. Placebo	0.98 (0.41-2.37)	1.12 (0.51-2.39)
Ibuprofen vs. Placebo	2.39 (0.69-8.64)	2.36 (0.82-6.75)
Diclofenac vs. Placebo	3.98 (1.48-12.7)	3.65 (1.42-10.73)
Celecoxib vs. Placebo	2.07 (0.98-4.55)	2.07 (1.07-4.33)
Etoricoxib vs. Placebo	4.07 (1.23-15.7)	3.66 (1.31-11.57)
Rofecoxib vs. Placebo	1.58 (0.88-2.84)	1.76 (1.03-3.06)

Lumiracoxib vs. Placebo	1.89 (0.64-7.09)	1.92 (0.71-5.23)
Death from any cause		
Naproxen vs. Placebo	1.23 (0.71-2.12)	1.26 (0.78-2.03)
Ibuprofen vs. Placebo	1.77 (0.73-4.30)	1.70 (0.78-3.78)
Diclofenac vs. Placebo	2.31 (1.00-4.95)	2.13 (1.07-4.15)
Celecoxib vs. Placebo	1.50 (0.96-2.54)	1.48 (0.97-2.30)
Etoricoxib vs. Placebo	2.29 (0.94-5.71)	2.01 (0.96-4.11)
Rofecoxib vs. Placebo	1.56 (1.04-2.23)	1.70 (1.23-2.34)
Lumiracoxib vs. Placebo	1.75 (0.78-4.17)	1.66 (0.81-3.52)
APTC outcome		
Naproxen vs. Placebo	1.22 (0.78-1.93)	1.23 (0.86-1.77)
Ibuprofen vs. Placebo	2.26 (1.11-4.89)	2.19 (1.21-4.01)
Diclofenac vs. Placebo	1.60 (0.85-2.99)	1.52 (0.90-2.54)
Celecoxib vs. Placebo	1.43 (0.94-2.16)	1.39 (1.01-1.95)
Etoricoxib vs. Placebo	1.53 (0.74-3.17)	1.46 (0.84-2.53)
Rofecoxib vs. Placebo	1.44 (1.00-1.99)	1.54 (1.17-2.03)
Lumiracoxib vs. Placebo	2.04 (1.13-4.24)	1.94 (1.19-3.29)

APTC, Antiplatelet Trialist Collaboration; n/e, not estimable

Influence of inclusion criteria

Both sensitivity analyses on the influence of our inclusion criteria confirmed the main analyses. Restricting the trials to studies with an accumulated number of myocardial infarction of at least 50 per NSAID changed the structure of the network because naproxen, ibuprofen, and lumiracoxib had only 26, 14, and 25 events accumulated. Between trial heterogeneity was low to moderate for all analyses (median τ^2 0.08; range 0.03-0.16).

Table 8: Results of sensitivity analyses on the influence of inclusion criteria

	Main analysis	**At least 500 patient-years per trial arm**	**At least 50 myocardial infarctions**
Myocardial infarction			
Patient-years	*117,218*	*105,816*	*85,056*
Accumulated events	*532*	*493*	*429*
Naproxen vs. Placebo	0.82 (0.37-1.67)	0.99 (0.39-2.38)	n/a
Ibuprofen vs. Placebo	1.61 (0.50-5.77)	1.61 (0.42-6.37)	n/a

Table 8: Results of sensitivity analyses on the influence of inclusion criteria

	Main analysis	At least 500 patient-years per trial arm	At least 50 myocardial infarctions
Diclofenac vs. Placebo	0.82 (0.29-2.20)	0.44 (0.08-1.87)	0.89 (0.30-2.47)
Celecoxib vs. Placebo	1.35 (0.71-2.72)	1.35 (0.63-3.03)	1.59 (0.85-3.28)
Etoricoxib vs. Placebo	0.75 (0.23-2.39)	0.40 (0.07-2.01)	0.81 (0.24-2.67)
Rofecoxib vs. Placebo	2.12 (1.26-3.56)	2.71 (1.46-5.47)	1.90 (1.08-3.22)
Lumiracoxib vs. Placebo	2.00 (0.71-6.21)	1.93 (0.47-7.57)	n/a
Stroke			
Patient-years	*115,770*	*105,814*	*84,627*
Accumulated events	*367*	*323*	*261*
Naproxen vs. Placebo	1.76 (0.91-3.33)	1.64 (0.75-3.85)	n/a
Ibuprofen vs. Placebo	3.36 (1.00-11.6)	3.02 (0.81-12.9)	n/a
Diclofenac vs. Placebo	2.86 (1.09-8.36)	2.17 (0.58-8.60)	2.78 (1.05-8.43)
Celecoxib vs. Placebo	1.12 (0.60-2.06)	1.11 (0.53-2.42)	1.16 (0.60-2.26)
Etoricoxib vs. Placebo	2.67 (0.82-8.72)	1.99 (0.44-8.38)	2.55 (0.79-8.80)
Rofecoxib vs. Placebo	1.07 (0.60-1.82)	1.01 (0.52-1.90)	0.89 (0.48-1.58)
Lumiracoxib vs. Placebo	2.81 (1.05-7.48)	2.32 (0.73-8.26)	n/a
Cardiovascular death			
Patient-years	*115,773*	*105,817*	*84,630*
Accumulated events	*294*	*255*	*217*
Naproxen vs. Placebo	0.98 (0.41-2.37)	1.01 (0.27-3.02)	n/a
Ibuprofen vs. Placebo	2.39 (0.69-8.64)	1.83 (0.34-8.74)	n/a
Diclofenac vs. Placebo	3.98 (1.48-12.7)	3.86 (0.78-24.68)	4.01 (1.38-14.6)
Celecoxib vs. Placebo	2.07 (0.98-4.55)	1.72 (0.60-5.23)	2.19 (0.96-5.51)
Etoricoxib vs. Placebo	4.07 (1.23-15.7)	3.92 (0.67-31.7)	4.05 (1.10-19.3)
Rofecoxib vs. Placebo	1.58 (0.88-2.84)	1.94 (0.81-4.42)	1.51 (0.70-3.09)
Lumiracoxib vs. Placebo	1.89 (0.64-7.09)	1.43 (0.25-6.68)	n/a
Death from any cause			
Patient-years	*114,118*	*103,904*	*82,975*
Accumulated events	*654*	*588*	*522*
Naproxen vs. Placebo	1.23 (0.71-2.12)	1.26 (0.69-2.27)	n/a
Ibuprofen vs. Placebo	1.77 (0.73-4.30)	1.41 (0.55-3.70)	n/a
Diclofenac vs. Placebo	2.31 (1.00-4.95)	1.73 (0.60-4.85)	2.28 (0.96-5.38)
Celecoxib vs. Placebo	1.50 (0.96-2.54)	1.27 (0.72-2.22)	1.52 (0.92-2.71)
Etoricoxib vs. Placebo	2.29 (0.94-5.71)	1.71 (0.57-5.35)	2.29 (0.82-6.28)
Rofecoxib vs. Placebo	1.56 (1.04-2.23)	1.75 (1.08-2.73)	1.58 (0.93-2.44)
Lumiracoxib vs. Placebo	1.75 (0.78-4.17)	1.37 (0.54-3.46)	n/a

Table 8: Results of sensitivity analyses on the influence of inclusion criteria

	Main analysis	At least 500 patient-years per trial arm	At least 50 myocardial infarctions
APTC outcome			
Patient-years	*116,334*	*105,814*	*802*
Accumulated events	*1056*	*958*	*85,081*
Naproxen vs. Placebo	1.22 (0.78-1.93)	1.24 (0.74-2.03)	n/a
Ibuprofen vs. Placebo	2.26 (1.11-4.89)	2.07 (0.93-4.54)	n/a
Diclofenac vs. Placebo	1.60 (0.85-2.99)	1.21 (0.52-2.80)	1.63 (0.83-3.18)
Celecoxib vs. Placebo	1.43 (0.94-2.16)	1.38 (0.87-2.23)	1.54 (0.97-2.50)
Etoricoxib vs. Placebo	1.53 (0.74-3.17)	1.16 (0.45-2.87)	1.56 (0.69-3.49)
Rofecoxib vs. Placebo	1.44 (1.00-1.99)	1.73 (1.17-2.59)	1.32 (0.85-1.96)
Lumiracoxib vs. Placebo	2.04 (1.13-4.24)	1.75 (0.84-3.71)	n/a

APTC, Antiplatelet Trialist Collaboration; n/a, not available

Influence of dose and outliers

Table 9 presents results on the influence of dose and outlying trials. Restricting the analysis to high-dose trials only showed the same results as the main analysis.

Between trial heterogeneity was low to moderate for all analyses (median τ^2 0.07; range 0.02-0.11).

Table 9: Results of sensitivity analyses on the influence of dose and outliers

	Main analysis	High-dose trials only	Outliers excluded
Myocardial infarction			
Patient-years	*117,218*	*105,360*	111,171
Accumulated events	*532*	*494*	531
Naproxen vs. Placebo	0.82 (0.37-1.67)	0.55 (0.20-1.56)	0.91 (0.40-1.88)
Ibuprofen vs. Placebo	1.61 (0.50-5.77)	1.61 (0.51-5.58)	1.91 (0.59-7.21)
Diclofenac vs. Placebo	0.82 (0.29-2.20)	0.79 (0.23-2.60)	0.86 (0.29-2.38)
Celecoxib vs. Placebo	1.35 (0.71-2.72)	1.53 (0.82-3.15)	1.48 (0.77-3.04)
Etoricoxib vs. Placebo	0.75 (0.23-2.39)	0.71 (0.19-2.72)	0.79 (0.23-2.63)

Table 9: Results of sensitivity analyses on the influence of dose and outliers

	Main analysis	High-dose trials only	Outliers excluded
Rofecoxib vs. Placebo	2.12 (1.26-3.56)	2.07 (1.23-3.58)	2.34 (1.36-4.22)
Lumiracoxib vs. Placebo	2.00 (0.71-6.21)	1.54 (0.46-5.77)	2.53 (0.89-8.84)
Stroke			No outliers
Patient-years	*115,770*	*105,100*	n/a
Accumulated events	*367*	*334*	n/a
Naproxen vs. Placebo	1.76 (0.91-3.33)	1.21 (0.48-3.15)	n/a
Ibuprofen vs. Placebo	3.36 (1.00-11.6)	2.70 (0.78-10.8)	n/a
Diclofenac vs. Placebo	2.86 (1.09-8.36)	5.25 (0.99-57.4)	n/a
Celecoxib vs. Placebo	1.12 (0.60-2.06)	1.15 (0.60-2.20)	n/a
Etoricoxib vs. Placebo	2.67 (0.82-8.72)	4.80 (0.77-55.2)	n/a
Rofecoxib vs. Placebo	1.07 (0.60-1.82)	0.87 (0.47-1.55)	n/a
Lumiracoxib vs. Placebo	2.81 (1.05-7.48)	1.98 (0.66-6.61)	n/a
Cardiovascular death			
Patient-years	*115,773*	*104,761*	110,272
Accumulated events	*294*	*273*	293
Naproxen vs. Placebo	0.98 (0.41-2.37)	0.90 (0.25-2.78)	1.00 (0.40-2.50)
Ibuprofen vs. Placebo	2.39 (0.69-8.64)	2.30 (0.57-8.92)	2.28 (0.63-8.35)
Diclofenac vs. Placebo	3.98 (1.48-12.7)	4.52 (1.18-22.3)	4.03 (1.45-12.4)
Celecoxib vs. Placebo	2.07 (0.98-4.55)	2.22 (0.96-5.56)	2.12 (1.06-4.74)
Etoricoxib vs. Placebo	4.07 (1.23-15.7)	4.37 (1.04-27.0)	4.02 (1.21-15.9)
Rofecoxib vs. Placebo	1.58 (0.88-2.84)	1.62 (0.81-3.20)	1.68 (0.89-3.16)
Lumiracoxib vs. Placebo	1.89 (0.64-7.09)	1.73 (0.45-6.98)	1.82 (0.58-6.25)
Death from any cause			
Patient-years	*114,118*	*103,106*	108,756
Accumulated events	*654*	*619*	653
Naproxen vs. Placebo	1.23 (0.71-2.12)	1.17 (0.55-2.28)	1.25 (0.73-2.14)
Ibuprofen vs. Placebo	1.77 (0.73-4.30)	1.70 (0.66-4.23)	1.75 (0.68-4.45)
Diclofenac vs. Placebo	2.31 (1.00-4.95)	2.00 (0.81-5.50)	2.39 (1.07-5.21)
Celecoxib vs. Placebo	1.50 (0.96-2.54)	1.49 (0.93-2.52)	1.54 (0.98-2.48)
Etoricoxib vs. Placebo	2.29 (0.94-5.71)	1.98 (0.72-6.03)	2.34 (1.01-5.95)
Rofecoxib vs. Placebo	1.56 (1.04-2.23)	1.64 (1.05-2.49)	1.63 (1.09-2.38)
Lumiracoxib vs. Placebo	1.75 (0.78-4.17)	1.58 (0.66-3.97)	1.74 (0.77-4.19)
APTC outcome			No outliers
Patient-years	*116,334*	*105,358*	n/a
Accumulated events	*1056*	*980*	n/a
Naproxen vs. Placebo	1.22 (0.78-1.93)	0.88 (0.47-1.73)	n/a

Table 9: Results of sensitivity analyses on the influence of dose and outliers

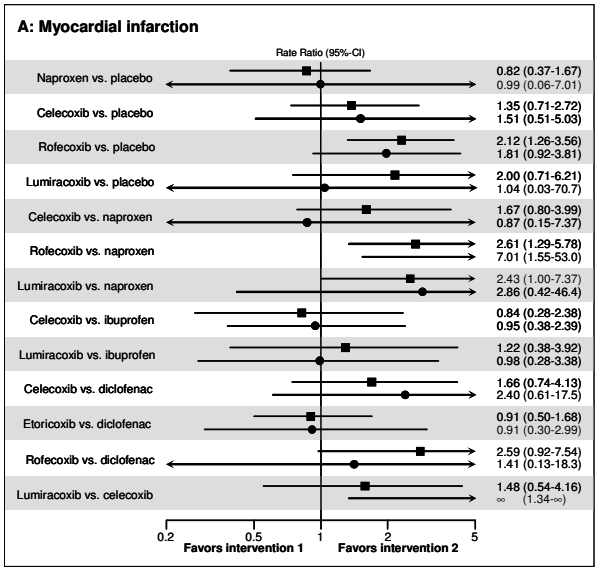
	Main analysis	High-dose trials only	Outliers excluded
buprofen vs. Placebo	2.26 (1.11-4.89)	2.01 (0.91-4.93)	n/a
Diclofenac vs. Placebo	1.60 (0.85-2.99)	1.65 (0.71-3.87)	n/a
Celecoxib vs. Placebo	1.43 (0.94-2.16)	1.50 (0.98-2.41)	n/a
Etoricoxib vs. Placebo	1.53 (0.74-3.17)	1.57 (0.61-4.10)	n/a
Rofecoxib vs. Placebo	1.44 (1.00-1.99)	1.38 (0.92-2.02)	n/a
umiracoxib vs. Placebo	2.04 (1.13-4.24)	1.59 (0.77-3.89)	n/a

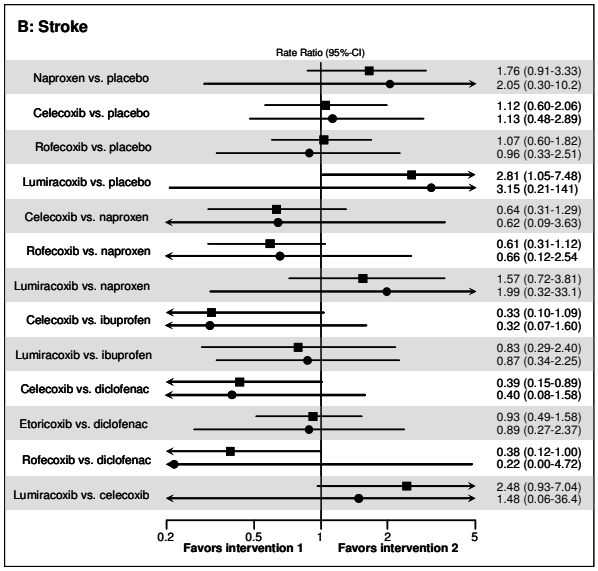
APTC, Antiplatelet Trialist Collaboration; n/a, not available

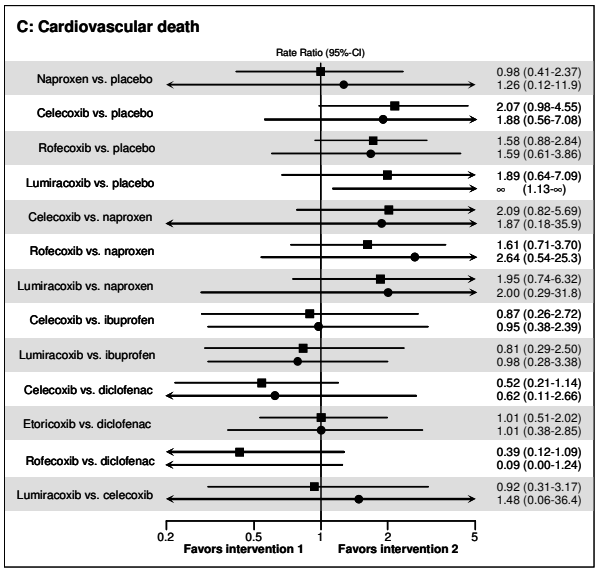
Comparison of results from network analysis and standard random-effects meta-analyses

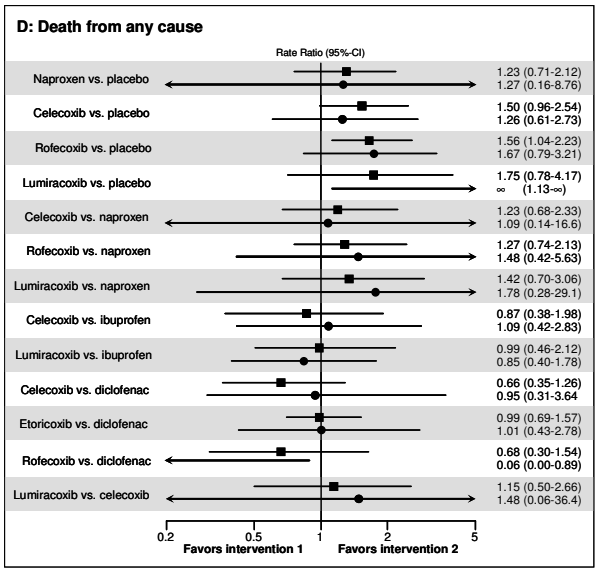
Figure 2 presents results of the network analysis (squares) and Bayesian random-effects meta-analyses (circles) accompanied by credibility intervals, respectively. Overall, for the comparisons available, both analysis agree in almost all cases. However, results of the network analysis usually show smaller credibility intervals.

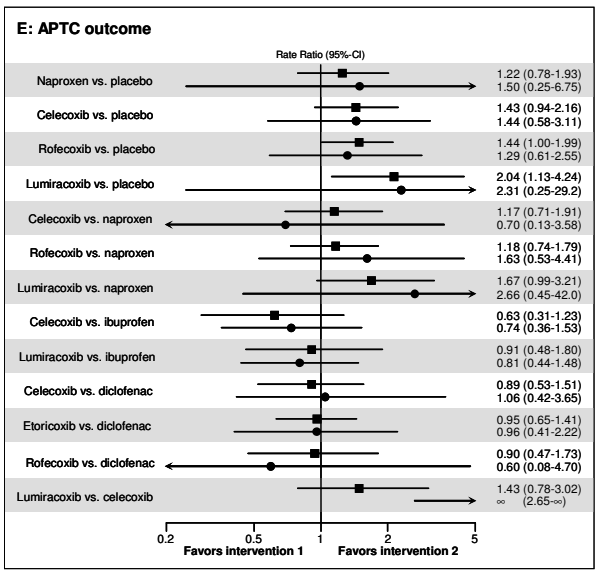
Figure 2: Comparison of results from network analysis and conventional meta-analyses











APTC, Antiplatelet Trialist Collaboration

Each square indicates the estimated rate ratio of each intervention compared to placebo with error bars indicating the corresponding 95%-credibility interval derived from the network meta-analysis. Dots and error bars indicating the corresponding 95% confidence intervals show the estimates derived from standard, pair-wise random-effects meta-analyses. Only direct pair-wise comparisons are shown to allow for comparing the different estimates.

A: Myocardial infarction			
	Rate ratio	Lower 95%-CI	Upper 95%-CI
Naproxen vs Placebo	0.82	0.37	1.67
Ibuprofen vs Placebo	1.61	0.50	5.77
Diclofenac vs Placebo	0.82	0.29	2.20
Celecoxib vs Placebo	1.35	0.71	2.72
Etoricoxib vs Placebo	0.75	0.23	2.39
Rofecoxib vs Placebo	2.12	1.26	3.56
Lumiracoxib vs Placebo	2.00	0.71	6.21
B: Stroke			
	Rate ratio	Lower 95%-CI	Upper 95%-CI
Naproxen vs Placebo	1.76	0.91	3.33
Ibuprofen vs Placebo	3.36	1.00	11.6
Diclofenac vs Placebo	2.86	1.09	8.36
Celecoxib vs Placebo	1.12	0.60	2.06
Etoricoxib vs Placebo	2.67	0.82	8.72
Rofecoxib vs Placebo	1.07	0.60	1.82
Lumiracoxib vs Placebo	2.81	1.05	7.48
C: Cardiovascular death			
	Rate ratio	Lower 95%-CI	Upper 95%-CI
Naproxen vs Placebo	0.98	0.41	2.37
Ibuprofen vs Placebo	2.39	0.69	8.64
Diclofenac vs Placebo	3.98	1.48	12.6
Celecoxib vs Placebo	2.07	0.98	4.55
Etoricoxib vs Placebo	4.07	1.23	15.7
Rofecoxib vs Placebo	1.58	0.88	2.84
Lumiracoxib vs Placebo	1.89	0.64	7.09
D: Death from any cause			
	Rate ratio	Lower 95%-CI	Upper 95%-CI
Naproxen vs Placebo	1.23	0.71	2.12
Ibuprofen vs Placebo	1.77	0.73	4.30
Diclofenac vs Placebo	2.31	1.00	4.95
Celecoxib vs Placebo	1.50	0.96	2.54
Etoricoxib vs Placebo	2.29	0.94	5.71
Rofecoxib vs Placebo	1.56	1.04	2.23
Lumiracoxib vs Placebo	1.75	0.78	4.17
E: APTC outcome			
	Rate ratio	Lower 95%-CI	Upper 95%-CI
Naproxen vs Placebo	1.22	0.78	1.93

Ibuprofen vs Placebo	2.26	1.11	4.89
Diclofenac vs Placebo	1.60	0.85	2.99
Celecoxib vs Placebo	1.43	0.94	2.16
Etoricoxib vs Placebo	1.53	0.74	3.17
Rofecoxib vs Placebo	1.44	1.00	1.99
Lumiracoxib vs Placebo	2.04	1.13	4.24