Supplementary file:

Efficacy and safety of celecoxib on the incidence of recurrent colorectal adenomas: A systematic review and meta-analysis.

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Date: 20-06-2018

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Table S1: The search strategy

	Search strategy	**Medline**	**Embase**
#1	(exp Colorectal Neoplasms/ OR exp Colonic Neoplasms/ OR exp Rectal Neoplasms/ OR exp Adenomatous Polyps/ OR exp Adenocarcinoma/ OR exp Intestinal Polyps/ OR exp Colonic Polyps/) OR ((colorectal cancer$.tw OR colorectal tumo$.tw OR colorectal neoplas$.tw OR colon cancer$.tw OR colon tumo$.tw OR colon neoplas$.tw OR colonic cancer$.tw OR colonic tumo$.tw OR colonic neoplas$.tw OR rectal cancer$.tw OR rectal tumo$.tw OR rectal neoplas$.tw OR rectum cancer$.tw OR rectum tumo$.tw OR rectum neoplas$.tw OR polyp$.tw OR adenoma$.tw OR adenomatous$.tw) OR (exp Adenoma/))	839926	867329
#2	exp CELECOXIB/ OR Cyclo-oxygenase inhibitor$.tw. OR Cyclooxygenase inhibitor$.tw. OR Cyclooxygenase 2 inhibitor$.tw. OR COX-2 inhibitor$.tw. OR COX-2 selective inhibitor$.tw. OR Coxib$.tw. OR celecoxib.tw.	18233	33765
#3	(randomized controlled trial.pt. OR controlled clinical trial.pt. OR exp Clinical Trial/ OR Randomized controlled trials/ OR random allocation/ OR double blind method/ OR single blind method/ OR clinical trial.pt. OR placebos/ OR placebo$.ti,ab. OR random$.tw OR blind$.ti,ab.)	1604174	2464837
#4	1 AND 2 AND 3	275	1566
#5	limit 4 to humans	237	1514
#6	limit 5 to exclude medline journals	NA	154
Total articles		391	

Figure S1: The PRISMA flow diagram

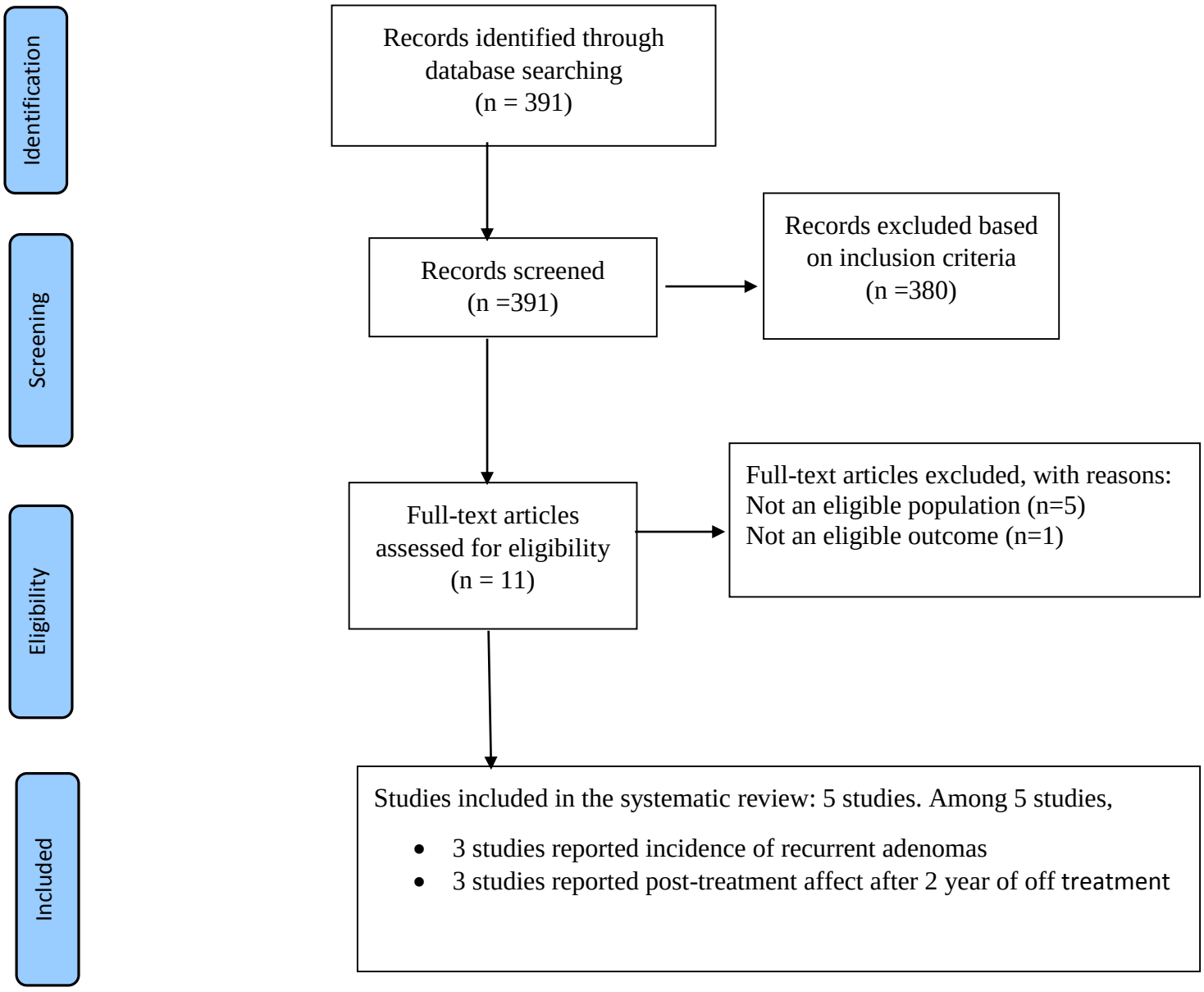


Table S2. Risk of bias assessment (Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) of RCTs reported incidence of recurrent adenomas

Author, year	Study	A	B	C	D	E	F
Arber, 2006	Pre SAP	+	+	+	+	+	+
Bertagnolli, 2006	APC	+	+	+	+	+	+
P. A. Thompson, 2016	Sel/Cel	+	?	-	+	+	+

A-Bias arising from the randomization process; B- Bias due to deviations from intended interventions; C- Bias due to missing outcome data; D- Bias in measurement of the outcome; E-Bias in selection of the reported result; F-Overall bias.

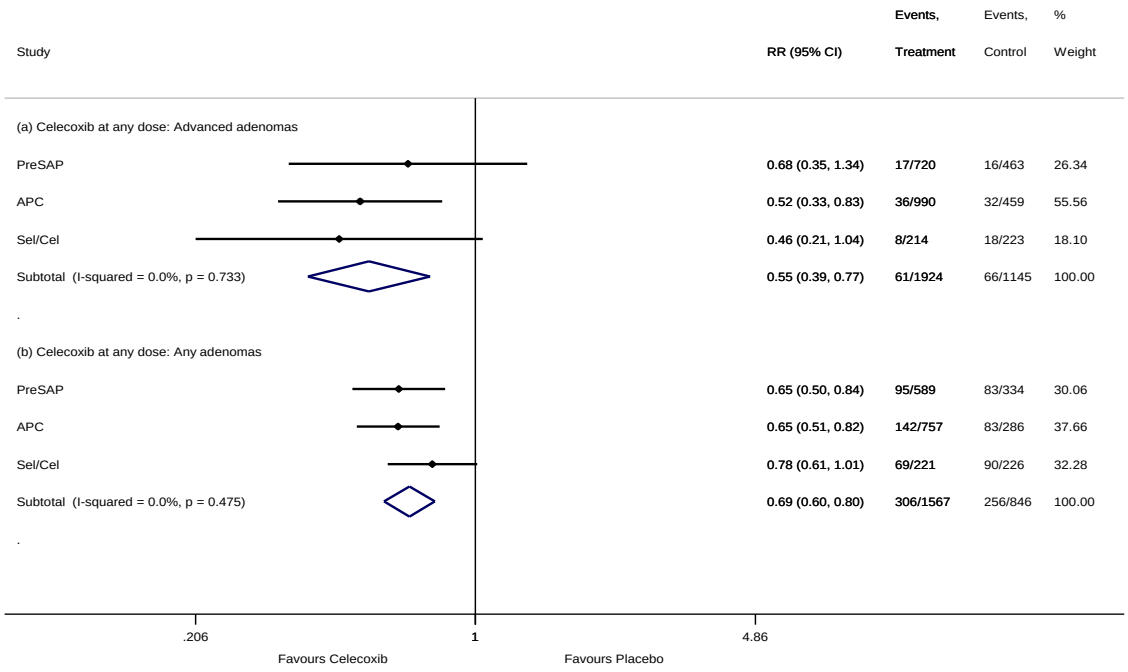
+symbol/green colour means 'low risk of bias'; symbol/yellow colour means 'some concerns'; -symbol/red colour means 'high risk of bias'

Sel/Cel:

Bias due to deviations from intended interventions: There were deviations from the intended interventions (in terms of adherence or use that were likely to impact on the outcome: "At the time celecoxib was suspended, 5.1% of the placebo arm and 3.1% of the celecoxib arm participants had completed taking the intervention"; adherence not clearly reported.

Bias due to missing outcome data: Differential missing data (different proportion of or different reasons for missing data in compared groups) at different time intervals. A high degree of missing data for the evaluation of primary outcomes (we used primary efficacy outcomes reported within 1 year of discontinuing intervention as reported by study authors)

Figure S2: Sensitivity analysis-per protocol completer analysis



Per protocol completer analysis; Sel/Cel: those subjects who underwent colonoscopy surveillance at the prespecified time period per protocol at 3.5 years (as per protocol follow-up duration is around 3-5 years).

Figure S3: Sensitivity analysis-fixed effect model

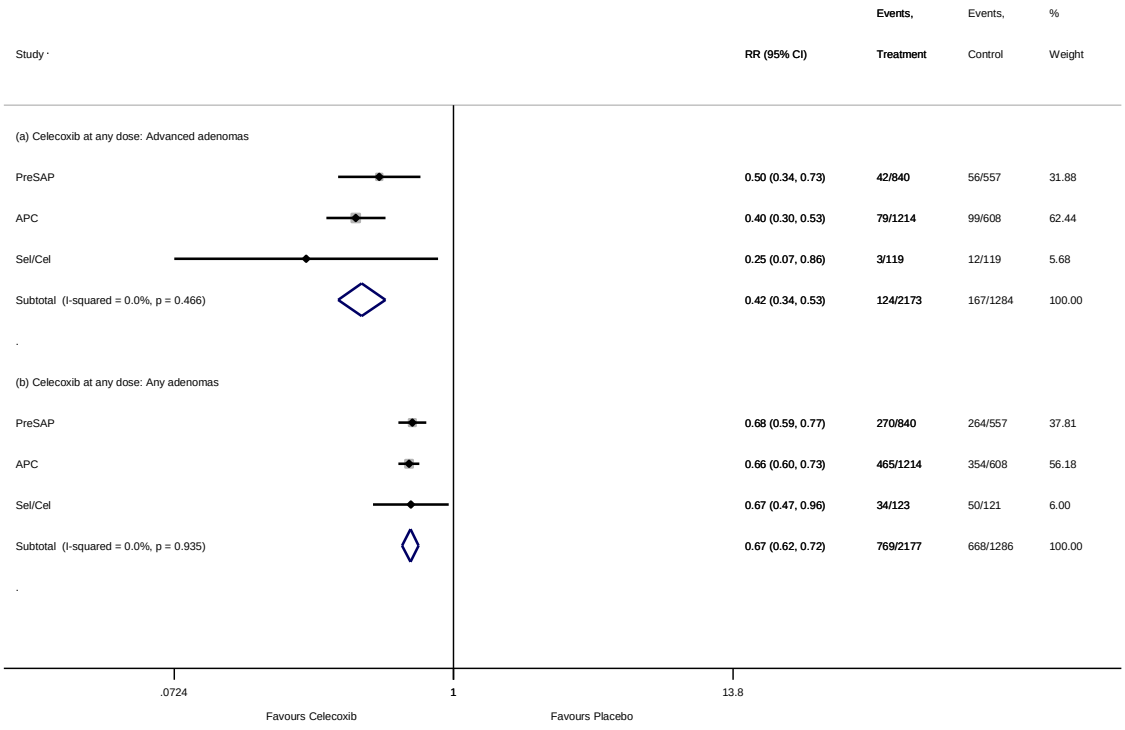


Figure S4: Sensitivity analysis-excluding high ROB trial

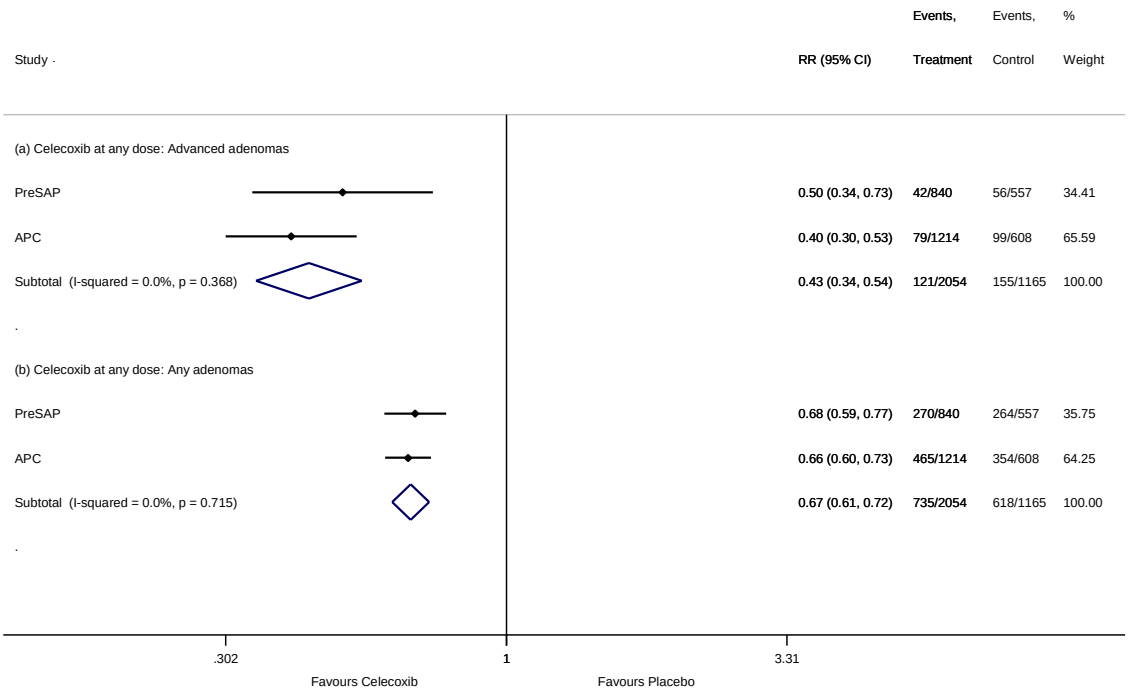


Figure S5: Subgroup analysis based on dosing frequency: primary outcomes

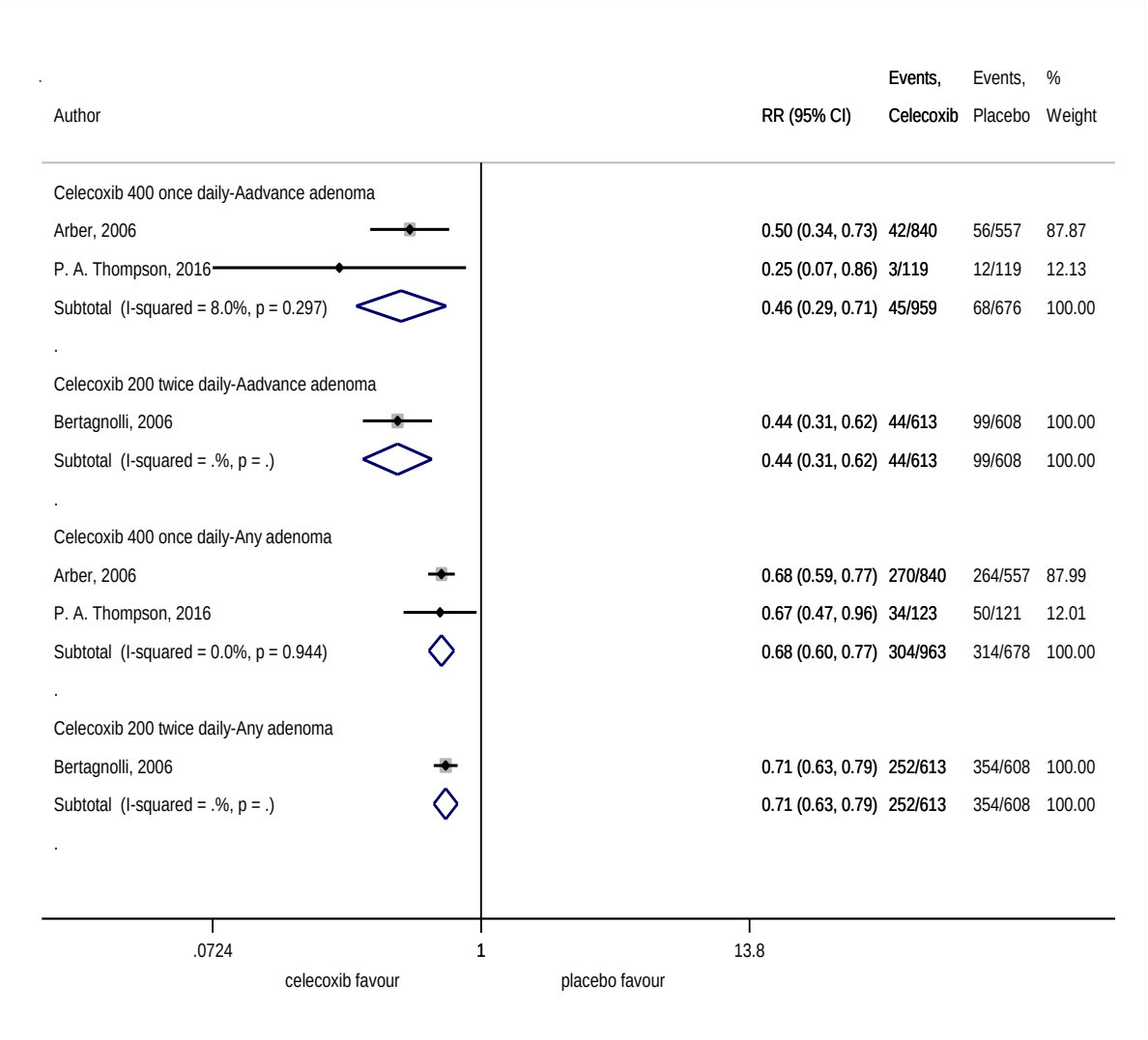


Figure S6: Subgroup analysis for safety outcomes: celecoxib 400 mg/day

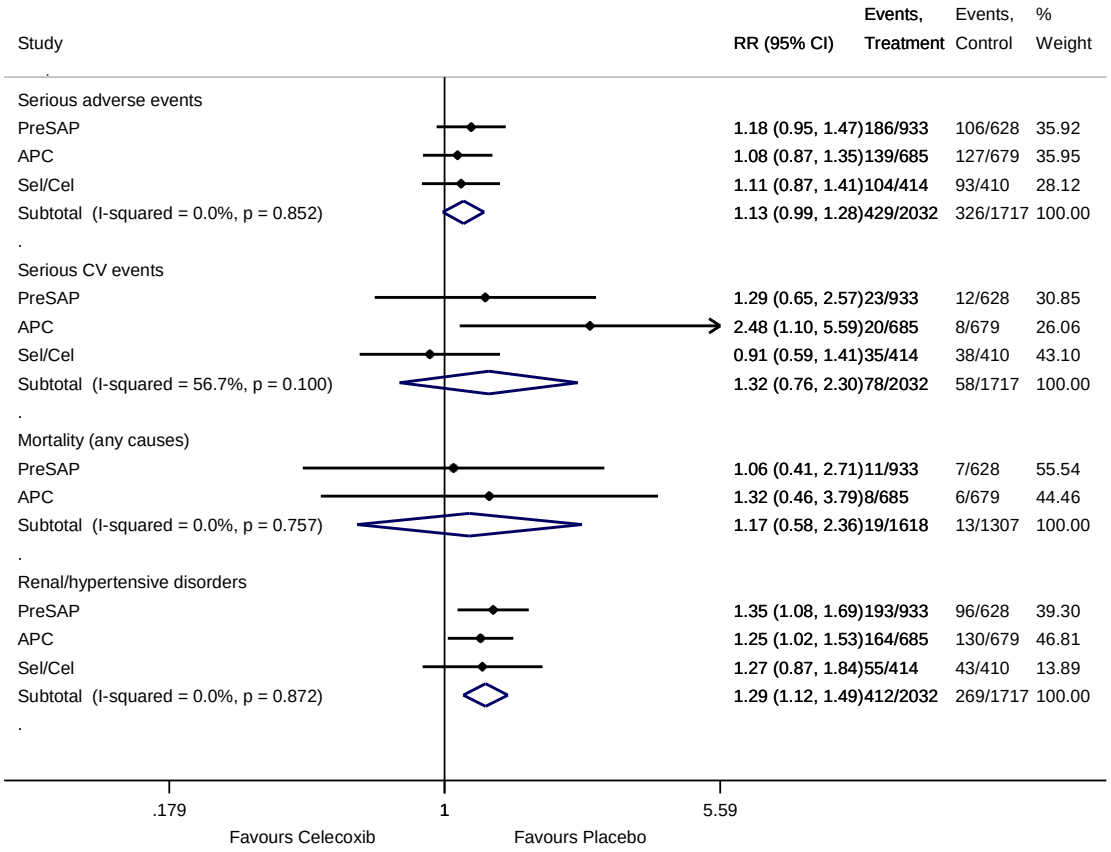


Figure S7: Subgroup analysis based on dosing frequency: safety outcomes

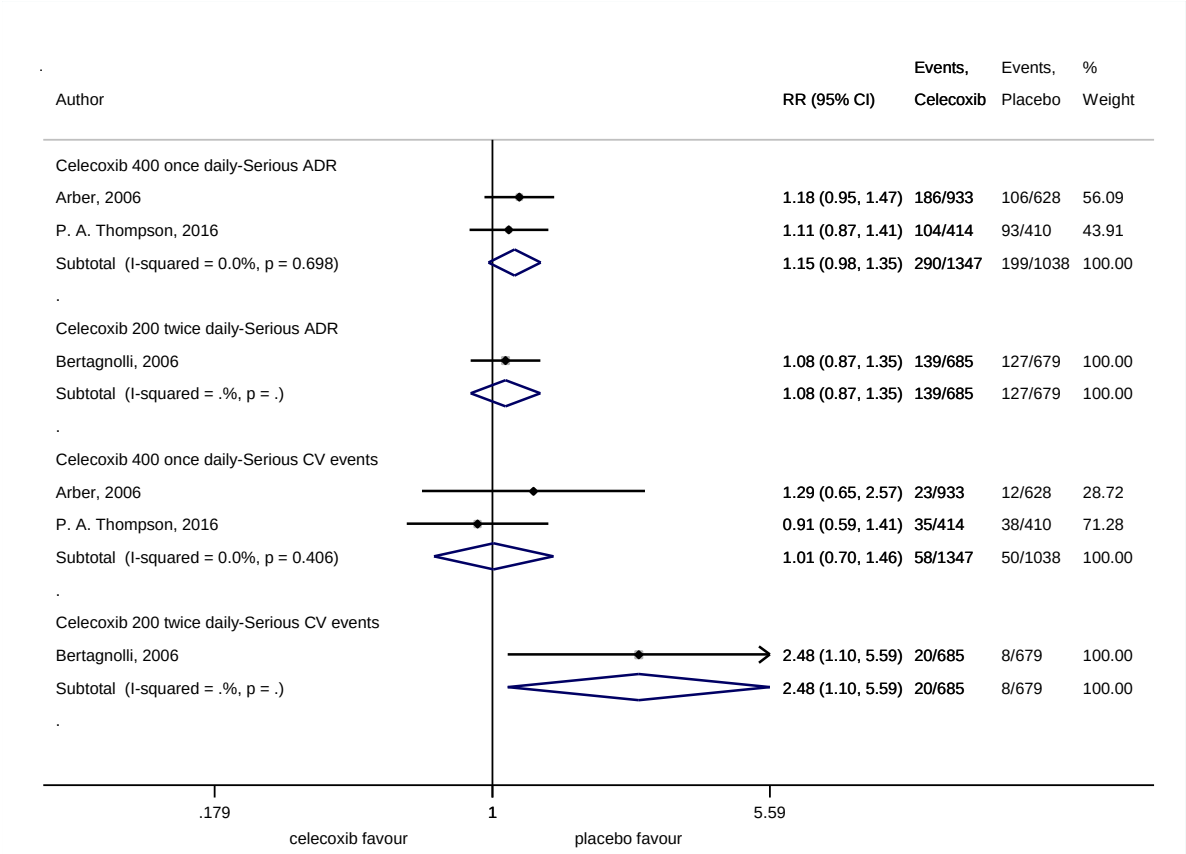


Table S3. GRADE Summary of evidence

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias[#]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**celecoxib 400mg/day**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Celecoxib at any dose: any adenomas (follow up: range 1 years to 3 years)											
3	randomised trials	not serious	not serious	not serious	not serious	none	769/2177 (35.3%)	668/1286 (51.9%)	**RR 0.67** (0.62 to 0.72)	**171 fewer per 1,000** (from 145 fewer to 197 fewer)	⊕⊕⊕⊕ HIGH
Celecoxib at any dose: advanced adenomas (follow up: range 1 years to 3 years)											
3	randomised trials	not serious	not serious	not serious	not serious	strong association [$]	124/2173 (5.7%)	167/1284 (13.0%)	**RR 0.42** (0.34 to 0.53)	**75 fewer per 1,000** (from 61 fewer to 86 fewer)	⊕⊕⊕⊕ HIGH
Celecoxib 400 mg/day: any adenomas (follow up: range 1 years to 3 years)											
3	randomised trials	not serious	not serious	not serious	not serious	none	556/1576 (35.3%)	668/1286 (51.9%)	**RR 0.69** (0.64 to 0.75)	**161 fewer per 1,000** (from 130 fewer to 187 fewer)	⊕⊕⊕⊕ HIGH
Celecoxib 400 mg/day: advanced adenomas (follow up: range 1 years to 3 years)											
3	randomised trials	not serious	not serious	not serious	not serious	strong association [$]	89/1572 (5.7%)	167/1284 (13.0%)	**RR 0.45** (0.35 to 0.58)	**72 fewer per 1,000** (from 55 fewer to 85 fewer)	⊕⊕⊕⊕ HIGH
Celecoxib at any dose: serious adverse events (follow up: range 1 years to 3 years)											
3	randomised trials	not serious	not serious	serious	not serious	none	583/2703 (21.6%)	326/1717 (19.0%)	**RR 1.15** (1.02 to 1.30)	**28 more per 1,000** (from 4 more to 57 more)	⊕⊕⊕◯ MODERATE
Celecoxib 400 mg/day: serious adverse events (follow up: range 1 years to 3 years)											
3	randomised trials	not serious	not serious	serious	serious *	none	429/2032 (21.1%)	326/1717 (19.0%)	**RR 1.13** (0.99 to 1.28)	**25 more per 1,000** (from 2 fewer to 53 more)	⊕⊕◯◯ LOW

#among three trials included in the analysis, Sel/Cel is considered to be at high ROB. Since, detection of significant changes in efficacy was not found for any outcomes after excluding Sel/Cel trial, we decided to grade our analysis as with no serious ROB; $ strong association, a RR<0.05 based on direct evidence, with no plausible confounders; *the 95% CI overlaps no effect

Table S4. Absolute anticipated benefits and risks of celecoxib for colorectal adenomas

Interventions	Anticipated absolute risk difference of advanced adenomas over 1-3 years per 1000 treated individuals (95% CI)		Anticipated absolute risk difference of adverse events over 1-3 years per 1000 treated individuals (95% CI)	
	Low-risk adenoma at baseline	High-risk adenoma at baseline	Serious adverse events	Cardiovascular events
Celecoxib 400 mg/day	-41 (-32 to -48)	-90 (-68 to -106)	-25 (-2 to 53)	11 (-8 to 44)
Celecoxib 800 mg/day	-49 (-30 to -56)	-108 (-82 to -124)	38 (0 to 95)	82 (19 to 186)
Celecoxib 400 mg once daily	-40 (-21 to -53)	-88 (-47 to 116)	29 (-4 to 67)	1 (-10 to 16)
Celecoxib 200 mg twice daily	-41 (-28 to -51)	-91 (-62 to -112)	15 (-25 to 67)	50 (3 to 156)

Low risk group includes patients with 1-2 small (<1 cm) tubular adenoma(s) with low grade dysplasia, and estimated risk of advanced adenomas of 74 per 1000 individuals without intervention; high risk group includes patients with 1 cm or larger, with villous or tubule-villous histology, with high grade dysplasia, and/or with intra-mucosal carcinoma or invasive cancer, and estimated risk of advanced adenomas of 163 per 1000 individuals without intervention.

Serious adverse events were defined as events resulting in death, hospital admission because of an adverse event, severe gastrointestinal bleeding, CV or non-CV complications, or discontinuation of intervention due to an adverse event or events that were defined as serious or severe by study authors. 190 per 1000 events graded as serious or severe by original study authors over same time period without any intervention.

Serious CV events defined as the composite of CV death, myocardial infarction, stroke, heart failure, thromboembolic event or defined as serious CV event by the study investigators. 34 per 1000 events graded as serious CV events by original study authors over same time period without any intervention.

Figure S8: Post-treatment effect on efficacy outcomes