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Research Article

Association between Non-Steroidal Anti-Inflammatory Drugs and The Risk of Recurrent Colorectal Adenomas: Renewed Meta-Analysis

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Abstract

Aim: Previous studies reported uncertain results on the relationship between non-steroidal anti-inflammatory drugs (NSAIDS) and colorectal adenomas. We performed a renewed meta-analysis investigating the efficacy and safety of NSAIDS in preventing the colorectal adenoma recurrence.

Methods: Data were retrieved from the Medicine, Cochrane library, and Emase database for randomized controlled trials (RCTs) up to August 2018. Data, bias, and quality were extracted and assessed by two independent reviewers. The random-effects model of Stata 12.0 was used for data analysis.

Results: This study included 13 RCTs. Aspirin and rofecoxib/celecoxib decreased the risk of recurrent adenomas with risk ratios (RR) of 0.83 (95% confidence interval (CI), 0.74-0.93, P=0.248, I2=26%, high-quality) and 0.63 (0.58-0.68, P=0.8, I2=0% high-quality), respectively. Subgroup analysis of 4- and 5-year follow-up for adenoma recurrence, respectively, 1.02 (0.84-1.24, P=0.127, I2=51.5% moderate-quality); and 1.15 (0.88-1.50, P=0.026, I2=72.6% very low-quality) and advanced adenomas, respectively, 0.88 (0.68-1.14, P=0.479, I2=0% high-quality); and 1.16 (0.82 -1.63, P=0.364, I2=1.0% high-quality).

Conclusion: NSAIDS decreased risks of recurrent adenomas, and results of 1- and 3-year follow-up were similar, but long-term 4- or 5-year follow-up showed that NSAIDS did not prevent the recurrence of adenomas. However, long-term rofecoxib and celecoxib were related to serious cardiovascular disorders and major bleeding; therefore, we suggest that the duration of rofecoxib and celecoxib prophylactic treatment for adenoma recurrence should not be more than 3 years.

Keywords: Non-steroidal anti-inflammatory drugs; Colorectal adenoma; Aspirin; Celecoxib; Rofecoxib; Meta-analysis

What Does This Paper Add to the Literature?

Our study first reports the pros and cons of long-term oral NSAIDs, and most benefits were achieved with short-term treatment of patients. Especially, we identified that the duration of administration should be limited to not more than 3 years, which paves the way for further research.

Introduction

Colorectal carcinoma is one of the most common malignancies, accounting for the second most cancer-related deaths in the US. In 2016, approximately two million new cancer cases and nearly 60,000 new related deaths occurred in the US [1]. Although the morbidity and mortality in patients over 50 years has decreased because of the improvements in diagnosis and treatment, an investigation shows that in patients less than 50 years it will double by 2030, especially in those 20-34 years old [2]. Adenomas are known to be precursors of colorectal cancer, especially those with a large diameter (≥1cm), which are villous, tubulovillous, and highly malignant. Early detection and removal of the tumors through colonoscopy can significantly decrease the risk of colorectal carcinoma [3]. However, the strict bowel cleansing required before a colonoscopy, dietary changes before and after colonoscopy, uncomfortable treatment, and the relatively high cost result in a low level of compliance [4]. The recurrence rate of adenomas would be high even if all adenomas are removed [5,6] and continual screening increases the social and economic burden, making prevention a major public health goal.

Systematic reviews and meta-analyses [7-12] published to date indicate that non-steroidal anti-inflammatory drugs (NSAIDS) could prevent the recurrence of colorectal adenoma. Because of factors such as small sample sizes, high heterogeneity, and different baseline characteristics, these studies have not reached a consensus on the relationship between NSAIDS and the recurrence of colorectal adenoma. Therefore, we performed a systematic review and meta-analysis including the most recent published papers to confirm the efficacy and safety of NSAIDS in preventing the recurrence of adenomas in patients with different baseline characteristics.

Methods

Screening strategy and inclusion criteria

The Medicine, Cochrane library, and Embase databases were screened up to August, 2018, and we retrieved all RCTs that reported the efficacy and safety of NSAIDS, and the risk of recurrent colorectal adenomas using the following Mesh or keywords "non-steroidal anti-inflammatory drugs," "adenoma*," "aspirin," "celecoxib," and "rofecoxib," and "random*." The language of studies was restricted to English. We manually retrieved the missing literature from the references in relevant meta-analyses and systematic reviews.

Two reviewers (Yin Wang and Qian Zhang) checked the retrieved studies to identify the missing data. All papers included in our research were selected based on the following inclusion criteria:

1. RCTs comparing NSAIDS with a placebo;
2. trials enrolling patients who had undergone a colonoscopy and had polyps detected and resected;
3. the primary endpoint was the recurrent incidence of adenomas, advanced adenomas (defined by one or more of the following features: ≥1.0 cm, with villous or tubulovillous tissue architecture, or high-grade dysplasia), or both;
4. follow-up of at least 1 year.

The exclusion criteria were

1. RCTS without a placebo or treatment group;
2. Letters, reviews, comments, case reports, and studies with lost statistical data; and
3. Participants who had history of familial adenomatous polyposis (FAP) and inflammatory bowel disease (IBD).

Risk bias assessment

Two authors (Yin Wang and Qian Zhang) independently assessed the risk of bias with all RCTs based on the Cochrane risk of bias criteria using RevMan (version 5.1) [13,14], and each quality item was graded as low-, high-, or unclear-risk. The seven items used to evaluate bias in each trial included the randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Evidence grading

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence of estimates (high, moderate, low, and very low) derived from meta-analyses using GRADE pro software. Reviewers independently assessed the confidence in effect estimates for all outcomes using the following categories: risk of bias, inconsistency, indirectness, imprecision, and publication bias [15,16].

Data extraction

Two researchers (Yin Wang and Qian Zhang) independently extracted the following data from every included trial: author, publication date, region, age, treatment duration, NSAIDS vs placebo, recurrent adenomas, and advanced adenomas. The third author made the final decision when there was any disagreement between the two researchers.

Statistical analysis

The association between NSAIDS and incidences of recurrent colorectal adenomas was identified. We performed a meta-analysis of the risk ratios (RRs), and 95% confidence intervals (Cis) using the Mantel-Haenszel test statistic. The Stata 12.0 software was used to pool the data with a random-effects model and detect heterogeneity using the I2 statistic. The I2 value ranged from 0 to 100% (0–25%, no heterogeneity; 25–50%, moderate heterogeneity; 50-75%, extensive heterogeneity; and 75-100%, serious heterogeneity [13]. All meta-analyses were performed using Stata 12.0 (version 12.0; College Station, TX, USA) and RevMan 5.1 (version 5.1; The Nordic Cochrane Centre, Copenhagen, Denmark). GRADE profiler (McMaster University, Hamilton, ON, Canada) was used to create the summary of findings table. All tests were two-tailed and a $P<0.05$ was considered statistically significant.

Results

Finally, 599 trials were finally screened, and 423 remained after duplicates were removed and 83 studies were identified after reading the titles and abstracts. The screening procedure yielded nine RCTS, reported in 13 publications (Figure 1). We considered eight publications accessing the same study at two different follow-up durations as a single study for all analyses. Figure 2 & 3 show the risk of bias assessments. All studies were clinical randomized double-blind controlled studies with high quality. Aspirin was administered in seven trials [17-23], rofecoxib in one [24], and celecoxib in the remaining [25-29]. Furthermore, low-dose aspirin (81mg/day) was included in two trials [18,19], 100mg/day in one trial [23], and 160mg/day in two trials, while high-dose aspirin (300mg/day) [20-22] and 325mg/day [17-19] was included in three trials each. Rofecoxib was administered at 25mg/day and celecoxib at 400 or 800mg/day, included in five [25-29] and two [25,26] trials, respectively. The follow-up times of these trials varied and included 1-5 years. The included trial characteristics are summarized in Table 1. The primary and secondary end points were the recurrence of any adenomas and advanced adenomas, and occurred in every trial.

Table 1: Characteristics of the included trials and participants.

Study	Region	Male No (%)	Age (Year)	Treatment Duration	NSAIDS vs Placebo	Recurrent Adenoma	Advanced Adenoma
Sandler RS [17]	USA	332 (52)	30-80	1y	asp:325mg/d n=317 pla: n=318	asp:43/259 pla:70/258	asp:7/259 pla:9/258

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Baron JA [18]	USA	712 (63.5)	21-80	3y	asp:81mg/d n=377 asp:325mg/d n=372 pla: n=372	asp:140/366 pla:160/355 pla:171/363	asp:28/366 pla:38/355 pla:47/363
Gravu MV [19]				4y	asp:81mg/d n=284 asp:325mg/d n=281 pla: n=285	asp:118/284 pla:138/281 pla=143/285	asp:26/284 pla:30/281 pla:38/285
Benamouzig R [20,21]	France	190(69.9)	18-75	1y	asp:81mg/d n=284 asp:325mg/d n=281 pla: n=285	asp:32/68 pla:33/60 pla:62/116	asp:12/68 pla:6/60 pla:18/116
				4y	asp:81mg/d n=284 asp:325mg/d n=281 pla: n=285	asp:15/55 pla:27/47 pla:33/88	asp:6/55 pla:4/47 pla:7/83
Logan RF [22]	UK	270 (57.6)	57.96	3y	asp:300mg/d n=434 pla: n=419	asp:99/434 pla:121/419	asp:41/434 pla:63/419
Ishikawa H [23]	Japan	246 (79.1)	40-70	2y	asp:100mg/d n=152 pla: n=159	asp:56/152 pla:73/159	asp:3/152 pla:4/159
Baron JA [24]	Western Countries	1602 (62.3)	40-96	1y	rof:25mg/ d n=1132 pla: n=1202	rof:287/1132 pla:471/1202	rof:86/1132 pla:152/1202
				3y	rof:25mg/ d n=1158 pla: n=1218	rof:460/1158 pla:646/1218	rof:141/1158 pla:213/2128
				4y	rof:25mg/ d n=561 pla: n=644	rof:105/561 pla:100/644	rof:45/561 pla:52/644
Bertagnolli MM [25,26]	USA, Australia, UK, Canada	1387 (68.2)	31-88	1y	cel:400mg/ d n=685 cel:800mg/ d n: 671 pla: n=679	cel:186/613 cel:137/601 pla:271/608	cel:26/613 cel:17/601 pla:37/608
				3y	cel:400mg/ d n=357 cel:800mg/ d n=400 pla: n=286	cel:66/357 cel:76/400 pla:83/286	cel:18/487 cel:18/503 pla:32/459
				5y	cel:400mg/ d n=207 cel:800mg/ d n=218 pla: n=214	cel:83/207 cel:90/218 pla:79/214	cel:12/207 cel:22/218 pla:11/214
Arber NA [27,28]	all around the world	1035 (66.3)	30-92	1y	cel:400mg/ d n=628 pla: n=933	cel:175/840 pla:181/557	cel:25/840 pla:40/557
				3y	cel:400mg/ d n=628 pla: n=933	cel:95/840 pla:83/334	cel:17/720 pla:16/463
				5y	cel:400mg/ d n=508 pla: n=347	cel:89/330 pla:30/184	cel:24/481 pla:12/315
Thompson PA [29]	USA	559 (67.9)	40-80	1y	cel:400mg/ d n=123 pla: n=121	cel:34/123 pla:50/121	cel:3/119 pla:12/119
				3y	cel:400mg/ d n=221 pla: n=336	cel:69/221 pla:90/226	cel:8/214 pla:18/226
				5y	cel:400mg/ d n=329 pla: n=336	cel:124/329 pla:135/226	cel:28/319 pla:32/332

asp: Aspirin; pla: Placebo; rof: Rofecoxib; cel: Celecoxib

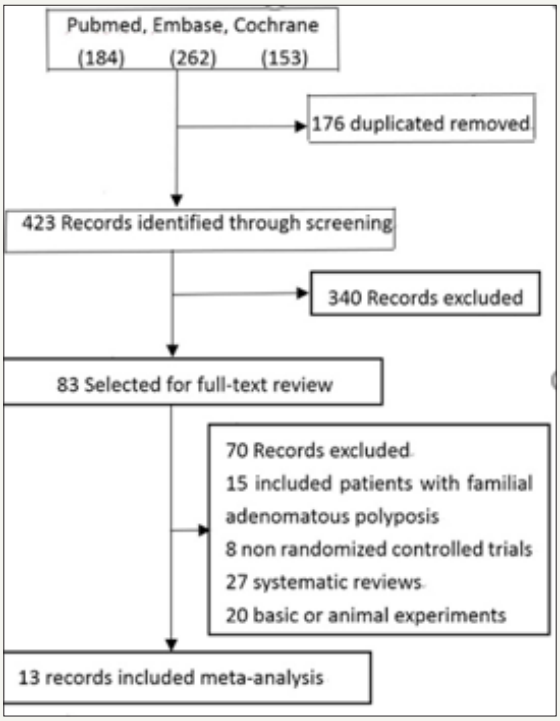

Figure 1: Study selection.

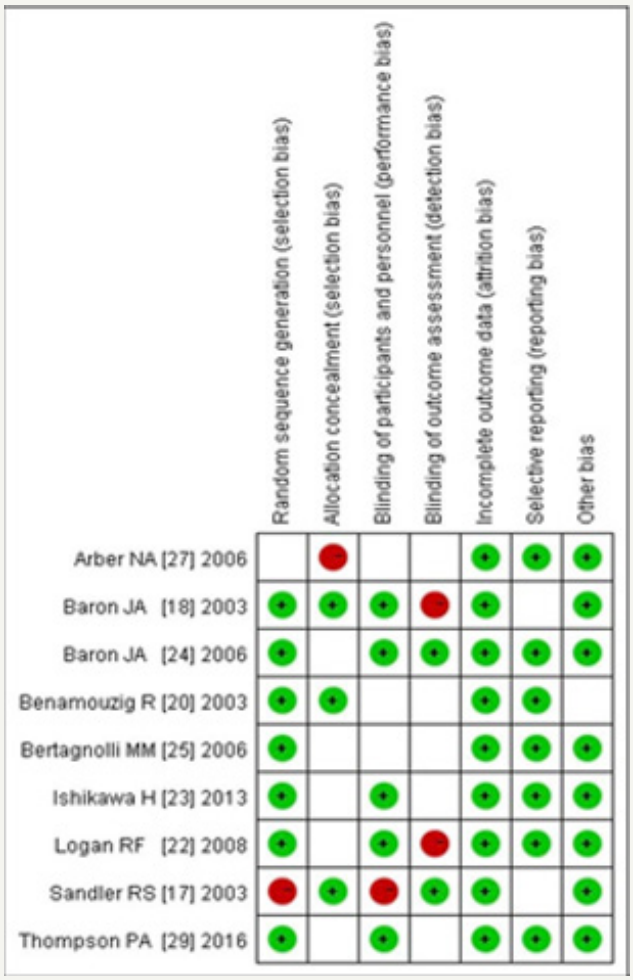

Figure 2: Bias risk map: a judgement of the percentage of all the projects that generate bias risk in the study.

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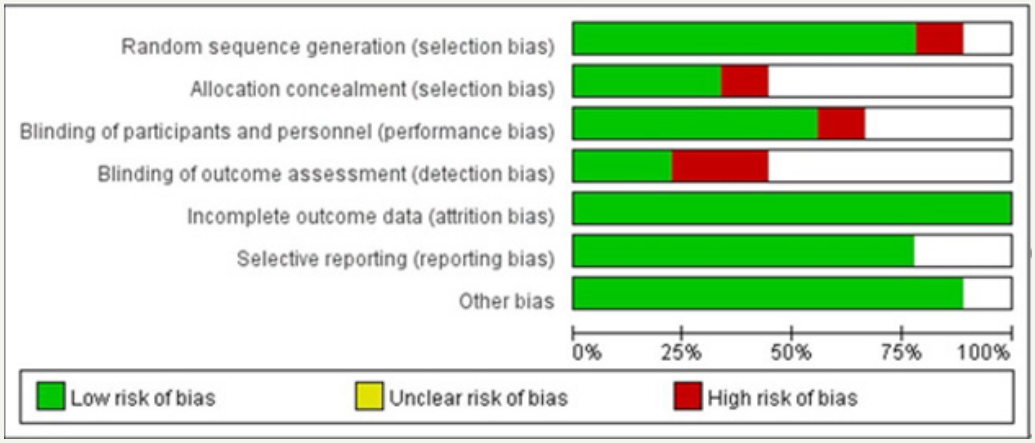

Figure 3: Bias risk map: the author's judgement of each bias risk item in all studies.

Recurrence of adenomas or advanced adenomas

Nine trials compared NSAIDS with a placebo. As shown in Figure 4 & 5, NSAIDS significantly decreased the recurrence of colorectal adenomas with RR=0.72 (95%CI, 0.64- 0.82, p<0.01, I^2=71.6%) and advanced adenomas, RR=0.62 (95%CI, 0.53 to 0.72, P=0.403, I^2=3.8%), for the high heterogeneity among the trials with the recurrence of adenomas. Subgroup analyses by the type of NSAIDS revealed that aspirin, rofecoxib, and celecoxib significantly decreased the recurrence of colorectal adenomas, with RR=0.83 (95%CI, 0.74-0.93, P=0.248, I^2=26%, high-quality) for aspirin and RR=0.63 (95%CI, 0.58-0.68, P=0.8, I^2=0% high-quality) for rofecoxib and celecoxib. While for the recurrence of advanced adenomas with low heterogeneity, the subgroup analysis by the type of NSAIDS revealed a significantly decreased in the recurrence of advanced adenomas with aspirin (RR=0.72 (95%CI, 0.57-0.90, P=0.767, I^2=0%, high quality)) and rofecoxib and celecoxib (RR=0.54 (95%CI, 0.43- 0.68, P=0.335, I^2=11.6% high-quality)) (Figure 4 & 5).

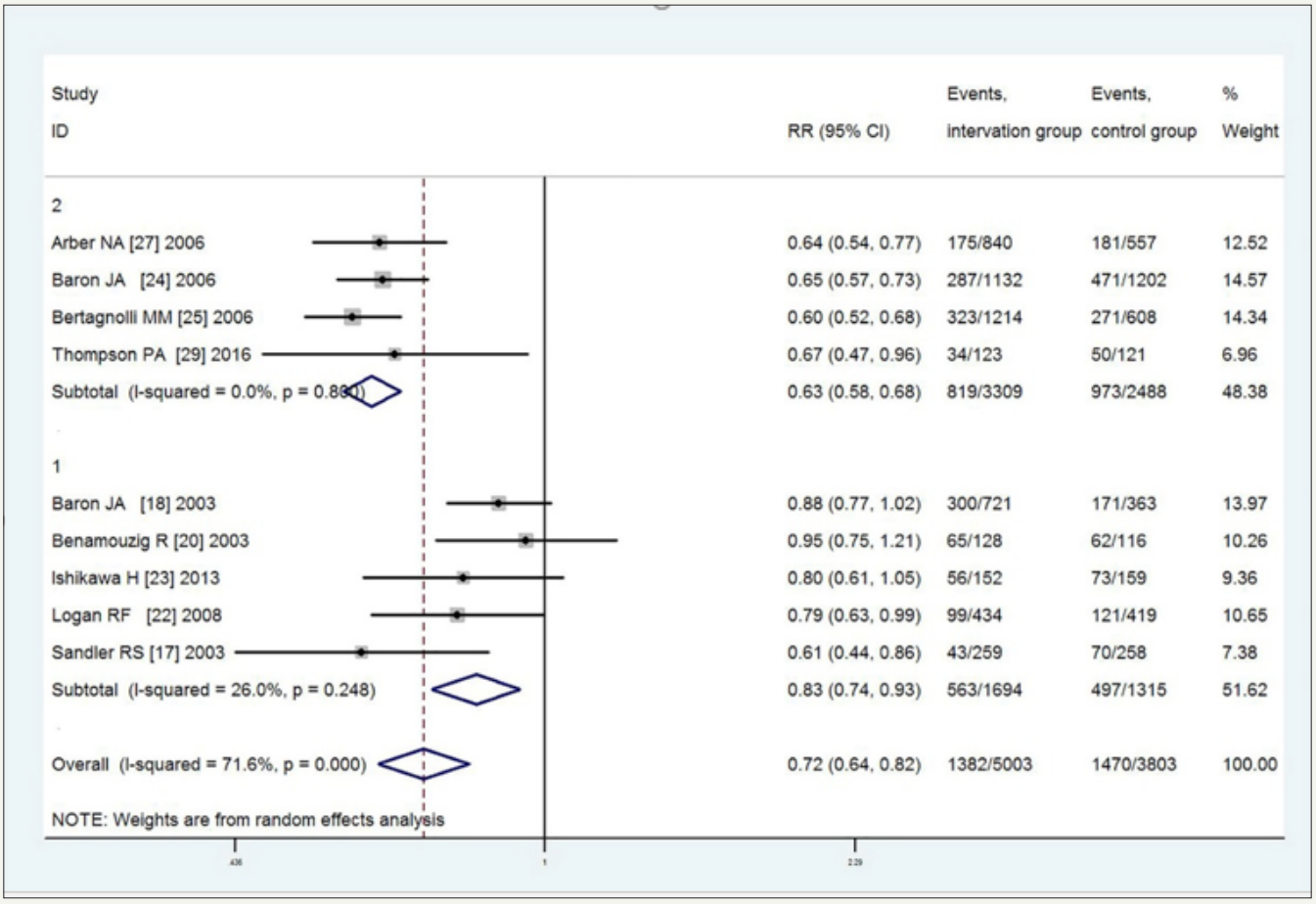

Figure 4: Random-effects model of RR of recurrence of adenomas to 1 and 2 vs placebo intervention (1: aspirin; 2: rofecoxib, celecoxib).

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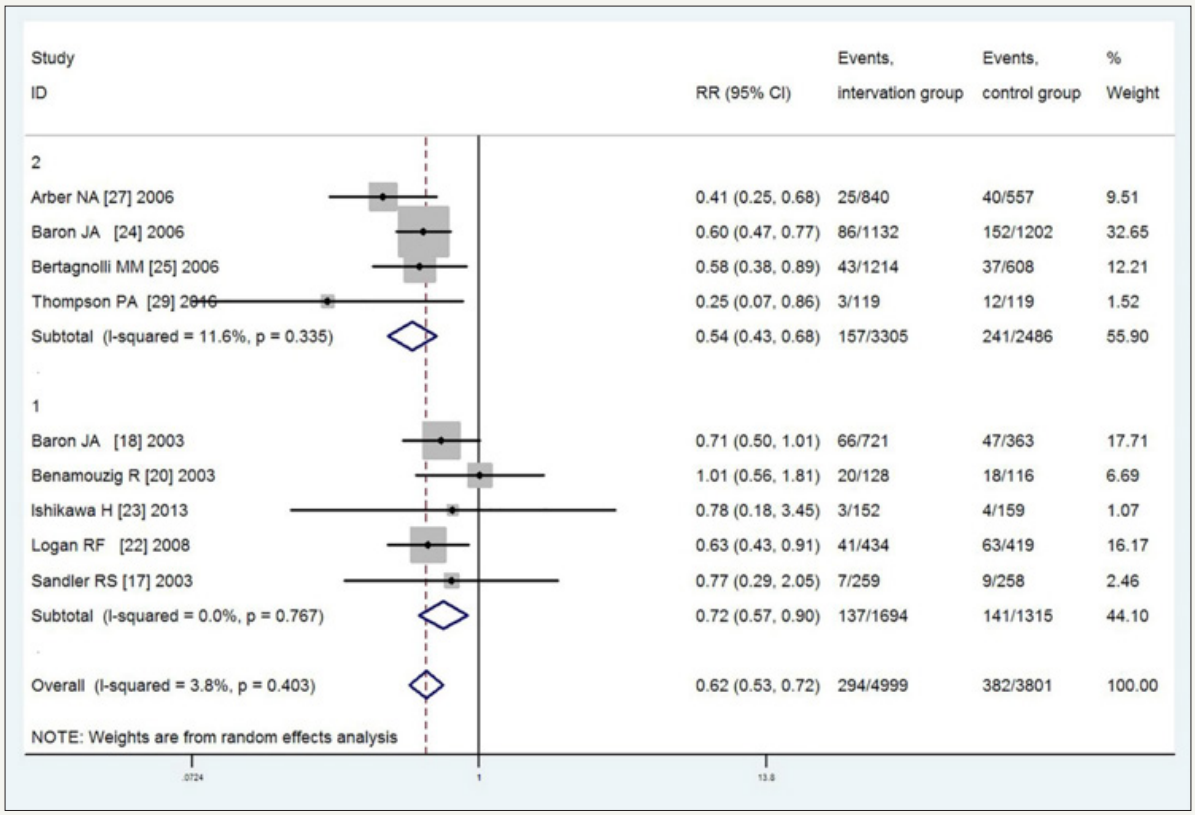

Figure 5: Random-effects model of RR of recurrence of advanced adenomas to 1 and 2 vs placebo intervention (1: aspirin; 2: rofecoxib, celecoxib).

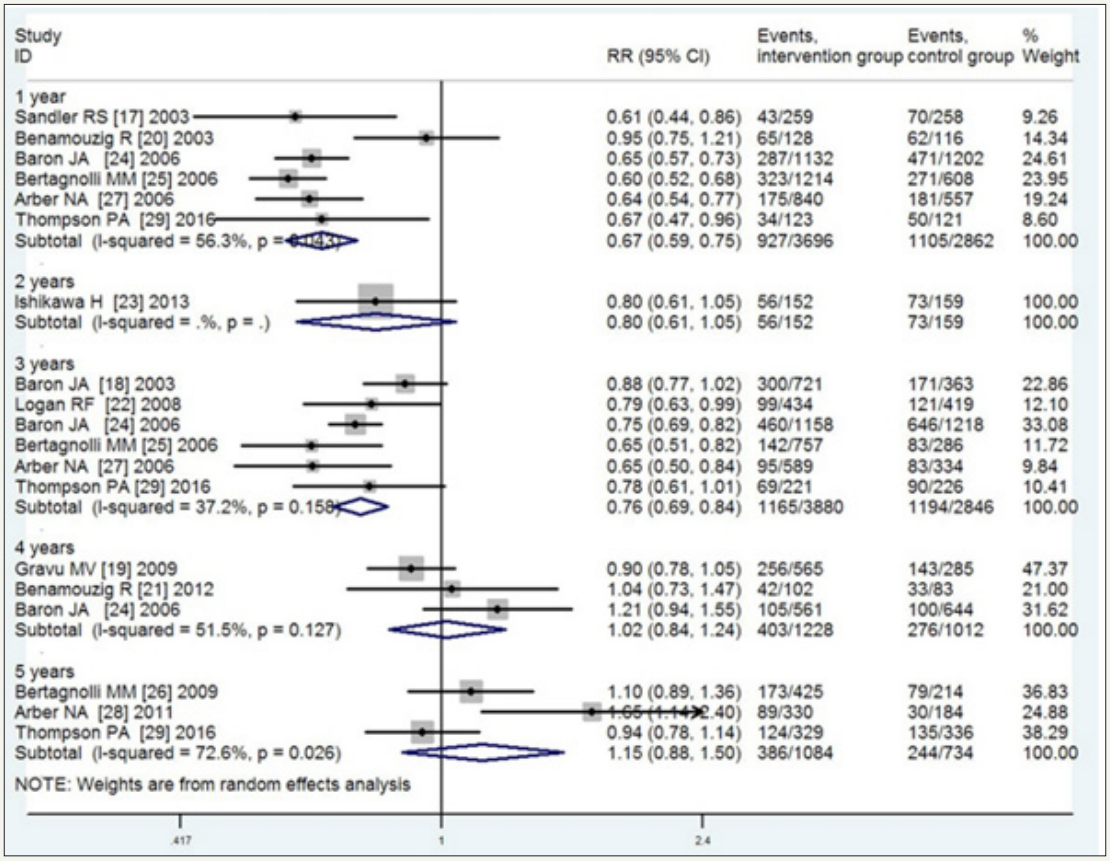

Figure 6: Incidence of recurrent adenomas with duration of follow-up time 1-year, 2-years, 3-years, 4-years and 5-years.

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Subgroup analysis of the risk of recurrent adenomas based on 1-, 2-, 3-, 4-, and 5-year follow-up periods, revealed RR=0.67 (95%CI, 0.59-0.75, P=0.043, I^2=56.3% moderate-quality), 0.80 (95%CI, 0.61-1.05, low-quality), 0.76 (95%CI, 0.69-0.84, P=0.158, I^2=37.2% high-quality), 1.02 (95%CI, 0.84-1.24, P=0.127, I^2=51.5% moderate-quality), and 1.15 (95%CI, 0.88-1.50, P=0.026, I^2=72.6% very low-quality), respectively. The corresponding values for advanced adenomas were 0.58 (95%CI, 0.46-0.73, P=0.295, I^2=18.3% high-quality), 0.78 (95%CI, 0.18-3.45, P=0.335, I^2=11.6% low-quality), 0.66 (95%CI, 0.57-0.76, P=0.816, I^2=0% high-quality), 0.88 (95%CI, 0.68-1.14, P=0.479, I^2=0% high-quality), and 1.16 (95%CI, 0.82-1.63, P=0.364, I^2=1.0% high-quality). These results indicated that with the extension of the follow-up, the efficacy of the NSAIDS in preventing the recurrence of adenomas and advanced adenomas gradually decreased, especially with the 4- and 5-year follow-up, and no significant interactions were observed between the NSAIDS and placebo. As shown in Figure 6 & 7, the significant heterogeneity in the recurrence of adenomas with the 1-, 4-, and 5-year follow-up was explainable by the type of NSAIDS. For the small sample, the analytical result of the 2-year follow-up was not precise (Figure 6 & 7).

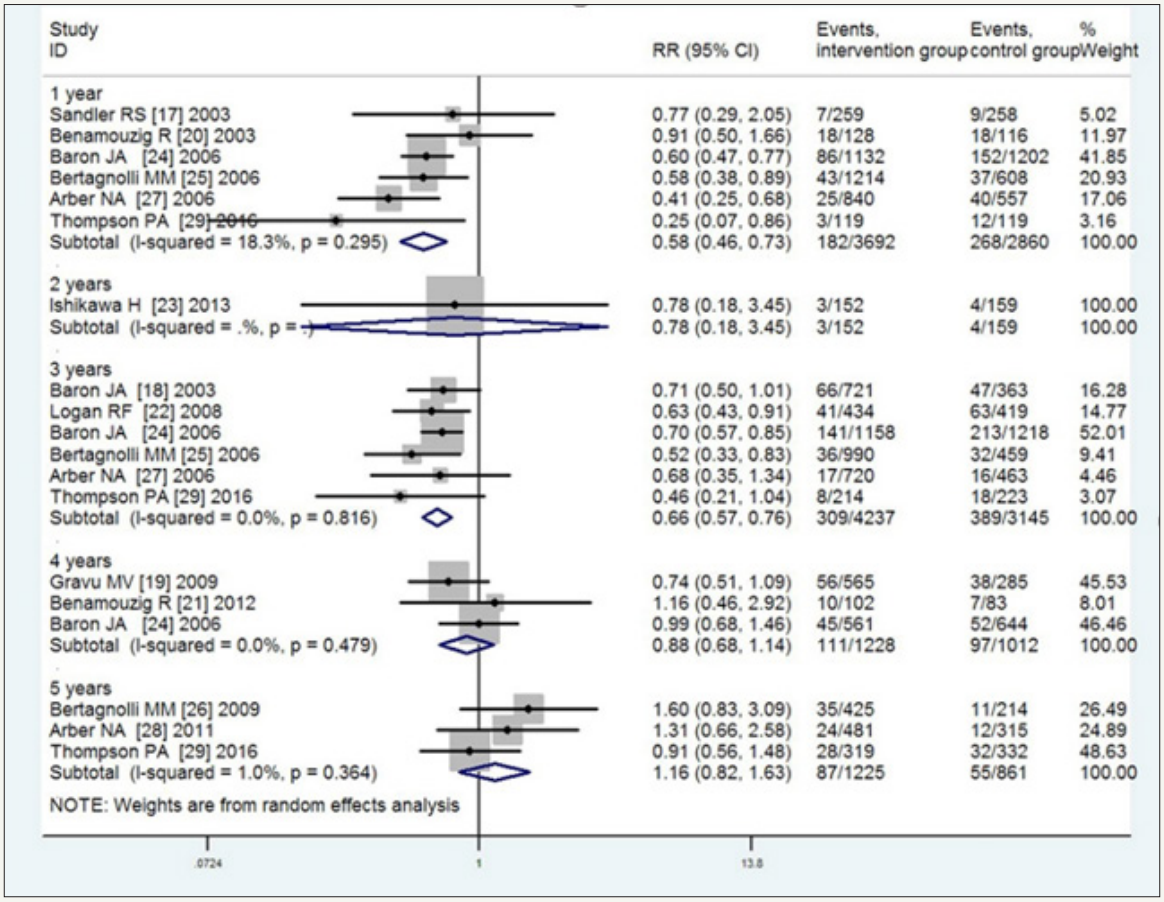

Figure 7: Incidence of recurrent advanced adenomas with duration of follow-up time 1-year, 2-years, 3-years, 4-years and 5-years.

Table 2: Summary of finding table about the quality of evidence of estimates*. The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

NSAIDS Compared to Placebo for Preventing the Recurrence of Colorectal Adenoma					
Bibliography					
Outcomes	**No of Participants (studies) Follow up**	**Quality of the Evidence (GRADE)**	**Relative Effect (95% CI)**	**Anticipated Absolute Effects**	
				Risk with Placebo	Risk difference with NSAIDS (95% CI)

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the recurrence of adenoma in aspirin	3009	⊕⊕⊕⊕	RR 0.83	Study population	
	(5 studies)	HIGH1	(0.74 to 0.93)	378 adenoma per 1000	64 fewer adenoma per 1000(from 26 fewer to 98 fewer)
	1-4 years	due to plausible counfounding would change the effect, dose-response gradient			
				Moderate	
				-	
the recurrence of advanced adenoma in aspirin	3009	⊕⊕⊕⊕	RR 0.72	Study population	
	(5 studies)	HIGH1	(0.57 to 0.9)	107 per 1000	30 fewer per 1000 (from 11 fewer to 46 fewer)
	1-4 years	due to plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of adenoma in rofecoxib and celecoxib stata 12.0	5797	⊕⊕⊕⊕	RR 0.63	Study population	
	(4 studies)	HIGH1	(0.58 to 0.68)	391 per 1000	145 fewer per 1000 (from 125 fewer to 164 fewer)
	1 years	due to plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of adveanced adenoma in rofecoxib and celecoxib stata 12.0	5791	⊕⊕⊕⊕	RR 0.54	Study population	
	(4 studies)	HIGH1	(0.43 to 0.68)	97 per 1000	45 fewer per 1000 (from 31 fewer to 55 fewer)
	1 years	due to large effect, plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of adenoma with 1-year follow-up stata 12.0	6558	⊕⊕⊕⊖	RR 0.67	Study population	
	(6 studies)	MODERATE1	(0.59 to 0.75)	386 per 1000	127 fewer per 1000 (from 97 fewer to 158 fewer)
	1 years	due to risk of bias, inconsistency, publication bias, plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of advanced adenoma with 1-yera follow-up stata 12.0	6552	⊕⊕⊕⊕	RR 0.58	Study population	
	(6 studies)	HIGH1	(0.46 to 0.73)	94 per 1000	39 fewer per 1000 (from 12 fewer to 61 fewer)
	1 years	due to risk of bias, imprecision, large effect, plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-

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The recurrence of adenoma with 2- years follow-up stata 12.0	311	⊕⊕⊖⊖	RR 0.80	Study population	
	(1 study)	LOW1	(0.61 to 1.05)	459 per 1000	92 fewer per 1000 (from 179 fewer to 23 more)
	2 years	due to risk of bias, imprecision, publication bias, plausible counfounding would change the effect			
				Moderate	
					-
The recurrence of advanced adenoma with 2-years follow-up stata 12.0	311	⊕⊕⊖⊖	RR 0.78	Study population	
	(1 study)	LOW1	(0.18 to 3.45)	25 per 1000	6 fewer per 1000 (from 21 fewer to 62 more)
	1 years	due to risk of bias, imprecision, publication bias, plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of adenoma with 3-years follow-up stata 12.0	6226	⊕⊕⊕⊕	RR 0.76	Study population	
	(6 studies)	HIGH1	(0.69 to 0.84)	420 per 1000	101 fewer per 1000 (from 67 fewer to 130 fewer)
	3 years	due to plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of advanced adenoma with 3-years follow-up	7382	⊕⊕⊕⊕	RR 0.66	Study population	
	(6 studies)	HIGH1	(0.57 to 0.76)	124 per 1000	42 fewer per 1000 (from 30 fewer to 53 fewer)
	3 years	due to plausible counfounding would change the effect			
				Moderate	
					-
The recurrence of adenoma with 4-years follow-up stata 12.0	2240	⊕⊕⊕⊖	RR 1.02	Study population	
	(3 studies)	MODERATE1	(0.84 to 1.24)	273 per 1000	5 more per 1000 (from 44 fewer to 65 more)
	4 years	due to risk of bias, publication bias, dose-response gradient			
				Moderate	
					-
The recurrence of advanced adenoma with 4-years follow-up stata 12.0	2240	⊕⊕⊕⊕	RR 0.88	Study population	
	(3 studies)	HIGH	(0.68 to 1.14)	96 per 1000	12 fewer per 1000 (from 31 fewer to 13 more)
	4 years				
				Moderate	
					-
The recurrence of adenoma with 5-years follow-up stata 12.0	1818	⊕⊖⊖⊖	RR 1.15	Study population	
	(3 studies)	VERY LOW1	(0.88 to 1.5)	332 per 1000	50 more per 1000 (from 40 fewer to 166 more)
	5 years	due to risk of bias, imprecision, publication bias, dose-response gradient			
				Moderate	
					-

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The recurrence of advanced adenoma with 5-years follow-up stata 12.0	2086	⊕⊕⊕⊕	RR 1.16	Study population	
	(3 studies)	HIGH1	(0.82 to 1.63)	64 per 1000	10 more per 1000 (from 11 fewer to 40 more)
	5 years	due to imprecision, dose-response gradient			
				Moderate	
					-
The recurrence of adenoma with low dose aspirin(80mg/d, 100mg/d, 160mg/d) stata 12.0	1224	⊕⊕⊕⊕	RR 0.82	Study population	
	(3 studies)	HIGH1	(0.72 to 0.94)	480 per 1000	86 fewer per 1000 (from 29 fewer to 134 fewer)
	1-3 years	due to plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of advanced adenomas with low dose aspirin(80mg/d, 100mg/d, 160mg/d) stata 12.0	1112	⊕⊕⊕⊕	RR 0.76	Study population	
	(3 studies)	HIGH1	(0.48 to 1.19)	121 per 1000	29 fewer per 1000 (from 63 fewer to 23 more)
	1-3 years	due to imprecision, plausible counfounding would change the effect, dose-response gradient			
				Moderate	
					-
The recurrence of adenomas with high dose aspirin(300mg/d, 325mg/d) stata 12.0	2264	⊕⊕⊖⊖	RR 0.85	Study population	
	(4 studies)	LOW1	(0.7 to 1.03)	367 per 1000	55 fewer per 1000 (from 110 fewer to 11 more)
	1-4 years	due to risk of bias, imprecision, publication bias, dose-response gradient			
				Moderate	
					-
The recurrence of advanced adenomas with high dose aspirin(300mg/d, 325mg/d) stata 12.0	2035	⊕⊕⊕⊕	RR 0.71	Study population	
	(4 studies)	HIGH1	(0.55 to 0.91)	134 per 1000	39 fewer per 1000 (from 12 fewer to 61 fewer)
	1-4 years	due to imprecision, plausible counfounding would change the effect			
				Moderate	
					-

CI: Confidence Interval; RR: Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1 No explanation was provided.

For low-dose aspirin (80, 100, and 160mg/day), the RR of the recurrence of any adenoma among three trials was 0.82 (95%CI, 0.72-0.94, P=0.88, I^2=0% high-quality), whereas the RR for the recurrence of advanced adenoma was 0.76 (95%CI, 0.48-1.19, P=0.275, I^2=22.6% high-quality). For high-dose aspirin (300 and 325mg/day), the RR for the recurrence of any adenoma among four trials was 0.85 (95%CI, 0.70-1.03, P=0.05, I^2=61.5% moderate-quality), whereas the RR for the recurrence of advanced adenoma was 0.71 (95%CI, 0.55-0.91, P=0.789, I^2=0% high-quality). The quality of the evidence of estimates was calculated using GRADE pro software and is shown in Table 2.

Adverse events

Table 3: The incidence of adverse events comparing COX-1 andCOX-2 with placebo.

Adverse Effect	No. of Trials	No. of Participants/Total (NSAIDS)	No. of Participants/Total (Placebo)	RR (95% CI)	P
Aspirin					
Death	4	28/1640	26/1225	0.75(0.44-1.28)	0.29
Cardiovascular Disorder	3	8/1323	4/907	1.37 (041-4.54)	0.6
Major Bleeding	3	46/1323	31/907	1.02 (0.85-1.59)	0.94
Refecoxib and celecoxib					
Death	4	43/3986	31/3014	1.05 (0.66-1.66)	0.839
Cardiovascular Disorder	4	251/3986	125/3014	1.54 (1.25-1.89)	<0.001
Major Bleeding	4	314/3986	167/3014	1.42 (1.91-1.71)	<0.001

For adverse events, several trials were reported in the meta-analysis, including death, myocardial infarction, and bleeding. For aspirin, the meta-analysis showed no significant differences compared with the placebo in death, myocardial infarction, and bleeding with RR of 0.75 (95%CI, 0.44-1.28, P=0.29), 1.37 (95%CI, 0.41-4.54, P=0.6), and 1.02 (95%CI, 0.85-1.59, Ph 0.94), respectively. While the incidences of death, myocardial infarction, and bleeding with rofecoxib and celecoxib compared with the placebo showed RRs of 1.05 (95%CI, 0.66-1.66, P=0.839), 1.54 (95%CI, 1.25-1.89, P<0.001), and 1.42 (95%CI, 1.19-1.71, P<0.001), and the results indicated that cyclooxygenase (COX)-2 may increase the risk of myocardial infarction and bleeding compared to the placebo (Table 3).

Discussion

This renewed meta-analysis included all high-quality RCTs and showed that aspirin, rofecoxib, and celecoxib could decrease the recurrence of adenomas and advanced adenomas. In addition, and the quality of evidence of estimates was high using GRADE pro software. Five subgroups with 1-, 2-, 3-, 4-, and 5-year follow-up, these results suggest that with the extension of follow-up, the NSAIDS showed less efficacy. Furthermore, there was no significant association of oral NSAIDS with decreased recurrence of adenomas and advanced adenomas with the 4- and 5-year follow-up. The quality of evidence of estimates was not consistent with that of a meta-analysis by Yin Wang et al. [9] reported that oral NSAIDS were significantly associated with increased risk recurrence of adenomas with follow-up >3 years. However, for the advanced adenomas, the results are consistent. Although the heterogeneities were significant with the >3-year follow-up in the two meta-analyses, the sample size of the 4- and 5-year follow-up of this current meta-analysis was almost three times that of the former meta-analysis, which indicates the strength, credibility, and accuracy of the results. However, higher quality randomized trials with longer follow-up durations comparing NSAIDS vs placebo are still needed to conclude our results.

Random-effects were used to pool data for the low-dose aspirin since randomization indicated a significant reduction in the risk of recurrent adenomas, and the quality of evidence of estimate was high. However, low-dose aspirin had no effect on recurrence of advanced adenomas, and the quality of evidence of estimate was high. This result was different from that of the study by Veettil et al. [11] who thought that low-dose aspirin had slight preventative effects on the recurrence of advanced adenomas. Information on prevention of recurrence of adenomas by high-dose aspirin showed it had no significant efficacy with substantial heterogeneity; however, a significant reduction was identified in the recurrence of advanced adenomas with no heterogeneity, and the quality of evidence of estimate was high. These results are consistent with those of Veettil et al [11]. However, because of the significant heterogeneity and limited sample size, additional studies with large sample sizes and high-quality randomized controlled trials should be designed to confirm the results.

The included studies reported on death, cardiovascular disorders, and bleeding events. The results comparing the aspirin and placebo groups were similar, to those of rofecoxib and celecoxib, in death, and no significant difference was observed between COX-2 and the placebo. However, the incidence of cardiovascular disorders and bleeding events were significantly higher in the rofecoxib and celecoxib groups than in the control group. The pooled summary indicated no significant reductions in the recurrence of adenomas and advanced adenomas for the 4- and 5-year follow-up, especially, the subgroup with the 5-year follow-up including participants who were all administered rofecoxib and celecoxib. From the above statistical analysis, long-term oral administration of rofecoxib and celecoxib did not significantly prevent the recurrence of colorectal adenomas and advanced adenomas. Furthermore,

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cardiovascular disorders and bleeding events caused by long-term oral administration of rofecoxib and celecoxib should be seriously considered as well as the appropriate duration for these agents that would provide the most benefits to patients. Therefore, future research studies should focus on these aspects.

Our research has numerous advantages. All RCTs that validated the benefits of NSAIDS in preventing the risk of recurrent colorectal adenomas were screened. The studies were well conducted with high compliance, high follow-up rates, and longer duration of time. The sample size in this meta-analysis was larger than that of the former. Thus, this analysis has high validity. Especially, the follow-up time in the included trials was sufficient to analyze the long-term effects of NSAIDS on the risk of recurrent adenomas and advanced adenomas, and this discovery has filled a knowledge gap in the field.

However, this analysis also has some shortcomings. First, with the 2-year follow-up, only one study showed aspirin have no efficacy on preventing the recurrence of adenomas and advanced adenomas, and the small sample size restricted the accuracy of the result. Second, our findings on the follow-up-response patterns are not convincing because of the high heterogeneity and small sample size and, therefore, the type and dose of NSAIDS may have an effect. Third, because of the low number of trials or insufficient sample size, we were unable to assess the dose-response of aspirin in preventing the incidence of recurrent and advanced adenoma.

In summary, this meta-analysis demonstrated that aspirin, rofecoxib, and celecoxib decreased the incidence of recurrent colorectal and advanced adenomas, and the quality of evidence of estimates was high. NSAIDS can significantly decrease the recurrence of adenomas and advanced adenomas with a 1- and 3-year follow-up, but with the long-term follow-up of 4- or 5-years, they have no preventative effects. Furthermore, long-term oral rofecoxib and celecoxib were associated with important cardiovascular disorders and major bleeding and, therefore, we suggest that the duration of oral rofecoxib and celecoxib for preventing adenomas should be restricted to no more than 3 years. However, because of the limited sample size and significant heterogeneity, the safety of long-term rofecoxib and celecoxib preventative treatment should be included in future considerations of the risks and benefits.

Author Contributions

Yin Wang: data collection, extraction, and analysis; writing the article. Qian Zhang: data analysis and modifying the article. Yao-Jun Wang: technology and method guidance, and handle differences.

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