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SYSTEMATIC REVIEWS AND META-ANALYSIS

Nonsteroidal Anti-inflammatory Drugs for Chemoprevention in Patients With Familial Adenomatous Polyposis: A Systematic Review and Meta-Analysis

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BACKGROUND AND AIMS: Published literature shows mixed reports of the benefits of nonsteroidal anti-inflammatory drugs (NSAIDs) on reducing colorectal polyps in patients with familial adenomatous polyposis (FAP). We conducted a systematic review and performed a meta-analysis to assess the impact of NSAIDs on colorectal polyp burden in patients with FAP. **METHODS:** We searched PubMed, EMBASE, and Cochrane for randomized controlled trials (RCTs) comparing the effect of NSAIDs vs placebo on the percent change in polyp number and polyp size in patients with FAP. Mean differences between the 2 study arms were pooled using RevMan. The risk of bias (RoB) was assessed using the Cochrane Risk of Bias tool for RCTs, and certainty in the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation methodology. **RESULTS:** The search strategy identified 1021 studies, out of which we included 8 RCTs with a total of 279 patients. Treatment for 6.4 ± 2.2 months with NSAIDs reduced polyp numbers by −17.4% (95% confidence interval −26.41%, −8.29%) (low certainty [I^2 89%] due to imprecision and issues with RoB) and polyp size by −15.9% (95% confidence interval −24.98%, −6.73%) (very low certainty (I^2 84%) due to imprecision, inconsistency, and issues with RoB). The most common gastrointestinal adverse events reported were stomatitis, diarrhea, and abdominal pain. Side effects leading to drug discontinuation were gastroenteritis and drug allergy. **CONCLUSION:** Short-term use of NSAIDs reduced polyp number and polyp size but with low to very low certainty of evidence. Further large multicenter studies are needed to further explore NSAIDs as a chemopreventive measure in patients with FAP.

Keywords: Familial Adenomatous Polyposis; Nonsteroidal Anti-Inflammatory Agent; Chemoprevention; Colorectal Cancer

Introduction

Familial adenomatous polyposis (FAP) results from a mutation in the adenomatous polyposis coli gene, which activates the adenoma-carcinoma sequence leading to numerous colorectal polyps starting at a young age.[1] Due to the anticipated inevitability of progression to colorectal cancer, the current practice is total colectomy or proctocolectomy to prevent colorectal cancer,[2] which has a significant impact on quality of life. However, alternative means of cancer interception in this population are needed because colorectal resection does not prevent neoplasia development in extracolonic organs. Also, the surgery is associated with significant morbidity and complications such as desmoid tumors.[3,4] Additionally, with the widespread advent of genetic testing, milder phenotypes of FAP are being discovered where colonoscopy, in combination with effective chemoprevention, could avoid surgery.

Previously, the investigators applied their knowledge of the basic biology of adenoma formation to conduct clinical trials to elucidate the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) as a pharmacologic chemopreventive strategy against FAP.[5] Cyclooxygenase (COX)-2, and prostaglandins have been independently implicated in the adenoma-to-carcinoma sequence.[5–7] Animal studies in which COX-2 deficiency was induced led to the suppression of adenomas.[8] By blocking COX-2, NSAIDs, including aspirin, inhibit the critical step in prostaglandin production.[8] In addition to COX inhibition, diverse COX-independent molecular and signal transduction pathways (involving nuclear factor kappa B) and disturbances of the inflammatory

Abbreviations used in this paper: **CI, confidence interval; FAP, familial adenomatous polyposis; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference; NSAIDs, nonsteroidal anti-inflammatory drugs; RCTs, randomized controlled trials; RoB, risk of bias.**

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microenvironment may be involved in the chemopreventive role of NSAIDs.[9] Nonselective NSAIDs also inhibit COX-1, which can increase the risk of mucosal injury. This led to clinical trials of selective COX-2 inhibitors in FAP.[10–12]

Combinations of NSAIDs with other drugs, such as difluoromethylornithine and ursodeoxycholic acid, have also been tested.[13,14] Besides NSAIDs, several other drugs are under investigation for chemoprevention, including erlotinib, obeticholic acid, and gusulekumab.[15–17] However, NSAIDs have been studied most extensively. Therefore, as new drugs are being tested, we conducted a systematic review and meta-analysis of the randomized controlled trials (RCTs) in patients with FAP to promote informed decision-making about NSAID use in this population and to report on the effect sizes of NSAID use on polyp number and size (surrogates for cancer development) against which the efficacy of newer chemopreventive agents can be measured. A few meta-analyses on this topic have been done in the past, but they suffered from the limitations of unclear inclusion criteria and lack of estimation of bias.[18–20] Also, the reviews did not report on side effects, an essential component of the informed decision-making process. We performed a meta-analysis to evaluate the impact of NSAIDs on the burden of colorectal polyps in patients with FAP. We did not perform a meta-analysis on the effects of NSAIDs on duodenal polyps because of a lack of studies that fulfilled our inclusion criteria. Our meta-analysis will not only help clinicians when they discuss nonselective (including aspirin) vs selective NSAIDs with their patients who have FAP but will also help the researchers in the field to design future high-quality studies by understanding the limitations of the prior studies.

Methods

This systematic review and meta-analysis were performed following the registered protocol available at http://www.crd.york.ac.uk/PROSPERO (registration ID: CRD42021247683) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[21]

Search strategy

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for published studies comparing the effects of NSAIDs vs placebo on colorectal polyp regression in patients with FAP. No language restriction was applied. The main text words and Medical Subject Heading/Entrée terms used for the search included: "nonsteroidal anti-inflammatory agent," "familial adenomatous polyposis," "cyclooxygenase 2 inhibitors," and "chemoprevention" (detailed search strategy is provided as Supplementary Data 1). The references of all included studies were screened for relevant studies.

Inclusion/exclusion criteria

Pre-established inclusion criteria were: 1) randomized controlled design with a placebo as the control arm; 2) use of selective, nonselective NSAIDs or aspirin; and 3) availability of full-length articles. We excluded studies with a nonrandomized design (eg, cohort, case-control, and case reports) and studies published as abstracts or conducted in animals. Detailed reasons for study exclusion are provided in Supplementary Data 2.

Study selection

Each study was independently evaluated for eligibility by 2 reviewers (U.F. and R.P.). All of the articles procured were downloaded into EndNote 7.0 (Thompson ISI Research Soft, Philadelphia, Pennsylvania, USA), a bibliographic database manager. Duplicate citations, if any, were identified and eliminated. All steps, including data abstraction, were conducted independently and in duplicate. A third reviewer (A.D.) verified and evaluated data extraction, and any disagreement was resolved by consensus with the senior author (A.B.). The screening results are illustrated in Figure 1 (PRISMA flowchart).

Outcomes

The predefined primary outcomes were the effects of NSAIDs on the percent change in colorectal polyp number and the percent change in mean colorectal polyp size compared to baseline. The secondary outcomes were adverse events of NSAID use in patients with FAP. We did not perform meta-analysis on the effects of NSAIDs on duodenal polyps because of lack of available data.

Quality assessment

The risk of bias (RoB) was assessed using the Cochrane Risk of Bias tool for RCTs.[22] Studies assessed using this tool are evaluated based on randomization, allocation concealment, blinding, and incomplete and/or selective reporting of results.

Certainty in the evidence

The certainty in the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for systematic reviews.[23] Using GRADE, certainty of evidence can be rated as either very low, low, moderate, or high. RCTs start as high certainty and can be downgraded due to the presence or suspicion of inconsistency/heterogeneity between studies, RoB in the primary studies, imprecision of the final results, indirectness of the evidence, and/or publication bias. We created a summary of the evidence table using GRADE- pro.[24] Two authors (A.E. and R.M.) assessed study quality, and any disagreement was resolved by consensus.

Data analysis

We abstracted the following information from studies: patient characteristics (age, gender, surgical history), NSAIDs used (name, dose), country, author, and publication date. We extracted in duplicate the percentage mean difference (MD) with the 95% confidence intervals (CI) using a random effect model. We pooled results across studies and created forest plots, when appropriate, using Review Manager (RevMan, version 5.4.1).[25] Drug-related adverse events were not reported uniformly among studies; hence, we summarized them qualitatively.

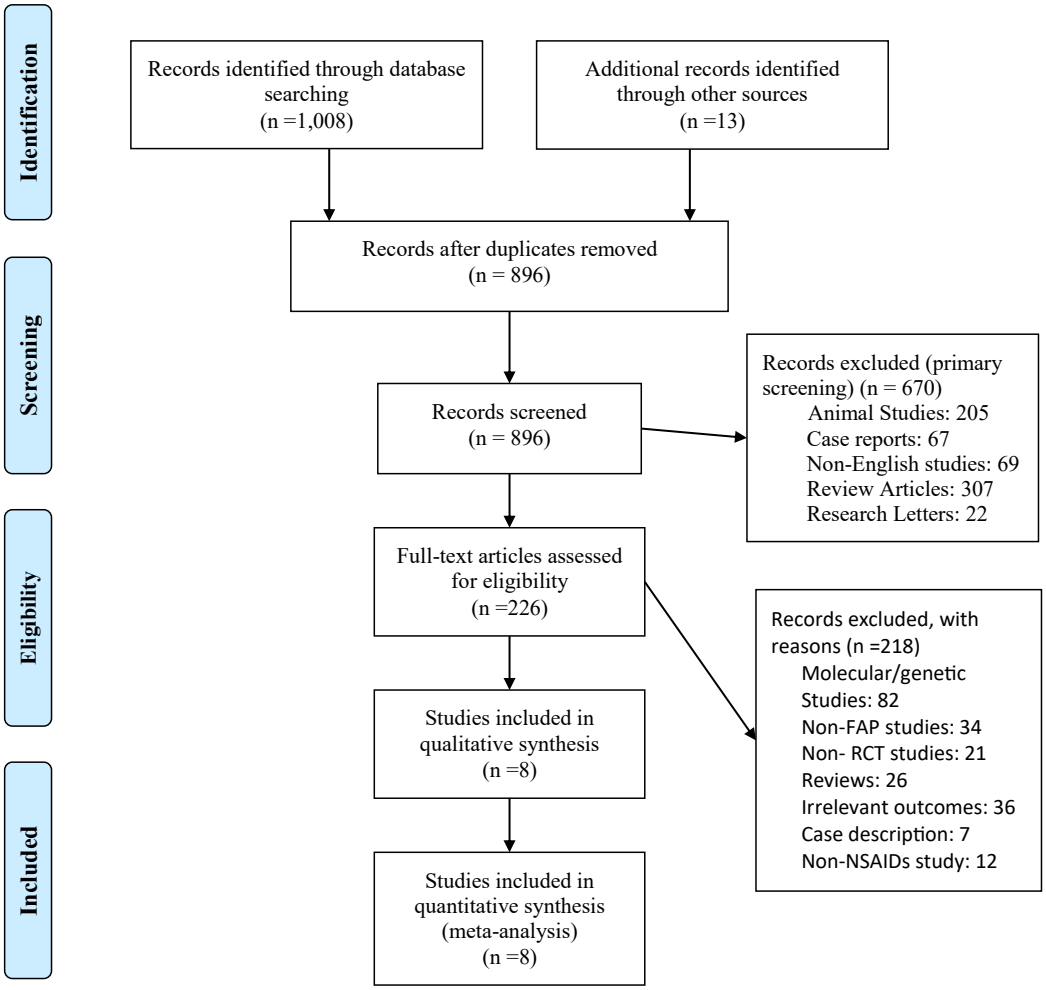

Figure 1. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Subgroup analysis

To explore the heterogeneity between studies, we conducted a post hoc subgroup analysis based on the type of NSAIDs: selective, nonselective, or aspirin.

Results

Patient characteristics

The search strategy identified 1021 studies, of which 8 RCTs with 279 patients met the inclusion criteria (Figure 1). Six RCTs informed colorectal polyp numbers and included 152 patients in the treatment arm and 118 patients in the control arm.[10–12,26–28] Five RCTs reported colorectal polyp size and included 142 patients in the treatment arm and 107 patients in the control arm.[10–12,26,28] The overall cohort included 49.3% females and had a mean age of 33.7 ± 6.6. At the start of the intervention, 71.5% had intact colon, whereas 28.5% had segmental colectomy, total colectomy, or proctocolectomy. The NSAIDs used were nonselective (Sulindac) and selective (Celecoxib, Tiracoxib, and Rofecoxib) in addition to aspirin (Table 1). The mean duration of NSAID treatment was 6.4 ± 2.2 months, and the mean duration of posttreatment follow-up was 7.4 ± 2.7 months.

Quality assessment

Based on the Cochrane's RoB tool, all 8 included studies were found to have high or unclear RoB in at least one domain (Supplementary Data 3). For instance, 6 studies did not provide randomization information,[10–12,26,27,29] and 5 did not report allocation concealment.[10,12,26,27,29] Based on the GRADE methodology, the certainty in the evidence was considered low to very low due to the presence of partially explained inconsistency between studies, high RoB in the included studies, and imprecision due to the low number of patients. (Supplementary Data 4).

Outcomes

Overall, treatment with NSAIDs compared to placebo reduced the polyp number (MD = −17.35%, (95% CI −26.41%, −8.29%); (low certainty (I^2 89%) due to imprecision and issues with RoB) and reduced the polyp size (MD = −15.85%, 95% CI −24.98%, −6.73%); (very low certainty (I2 84%) due to imprecision, inconsistency,

Table 1. Study Characteristics[b]

Author/Study	Population	Colectomy status	Intervention drug	Intervention period (follow-up duration), mo	Posttreatment endoscopy surveillance interval[c]	Groups	N	Age, mean, y	Female, %	Percent change in polyp number[d]	Percent change in polyp diameter[d]	Gastrointestinal adverse events
Labayle et al 1991[29]	Clinical history of FAP	Yes	Sulindac	4 (9)	Every 4 mo	100 mg TID Placebo	10 10	36.9 36.9	20 20	NR	NR	NR
Nugent et al 1993[30]	Clinical history of FAP	Yes	Sulindac	6 (6)	Every 6 mo	200 mg BID Placebo	12 12	NR NR (45 overall)	NR NR	NR	NR	NR
Giardiello et al 1993[26]	Patients recruited from FAP registry	Yes[a]	Sulindac	9 (12)	Every 3 mo	150 mg BID Placebo	11 11	21.9 26.3	54.54 63.63	−56 +70	−65.0 +10	NR
Keller et al 1999[27]	Clinical history of FAP	Yes[a]	Sulindac	3 (3)	Every 3 mo	150 mg BID Placebo	10 11	26.5 22.7	70 45.5	−46 +13	NR NR	NR
Steinbach et al 2000[10]	FAP proven by genetic testing	No	Celecoxib	6 (6)	Every 6 mo	400 mg BID 100 mg BID Placebo	30 32 15	31.1 38.6 39.9	40.0 46.9 40.0	−28 −11.9 +4.5	−30.7 −14.6 −4.9	Diarrhea, abdominal pain, dyspepsia
Higuchi et al 2003[11]	Observation of >100 colorectal adenomas	Yes[a]	Rofecoxib	9 (9)	Every 3 mo	25 mg daily Placebo	12 9	32.2 33.6	41.7 55.6	−6.8 +3.1	−16.2 +1.5	Stomatitis, abdominal pain, gastroenteritis
Iwama et al 2006[12]	Observation of >100 colorectal adenomas	No	Tiracoxib	6 (6)	Every 6 mo	200 mg daily 150 mg daily Placebo	19 21 20	31.5 38.8 35.2	68.4 42.9 60.0	0 +1 +6	+4.0 +3.0 +4.0	Stomatitis, diarrhea, stomach-ache
Ishikawa et al 2013[28]	Observation of >100 colorectal adenomas or germ line mutation	Yes[a]	Aspirin	8 (8)	Every 6 mo	100 mg daily Placebo	17 17	39.7 36.7	53 47	−22.69 0	−34/34 −20.78	Gastrointestinal ulcer, anemia

N, number of patients; NR, not reported; TID, three times a day; BID, twice a day; FAP, familial adenomatosis polyposis; APC, adenomatous polyposis coli.
[a]Study had both kinds of patients with entire colon present as well as who underwent colectomy with ileorectal anastomosis.
[b]Only randomized placebo controlled trials were included. All trials were conducted in an outpatient setting.
[c]Endoscopic modalities included rectoscopy, sigmoidoscopy, or colonoscopy in the included studies.
[d]Primary outcomes were qualitative or quantitative changes in polyp number or size or both, depending on the study.

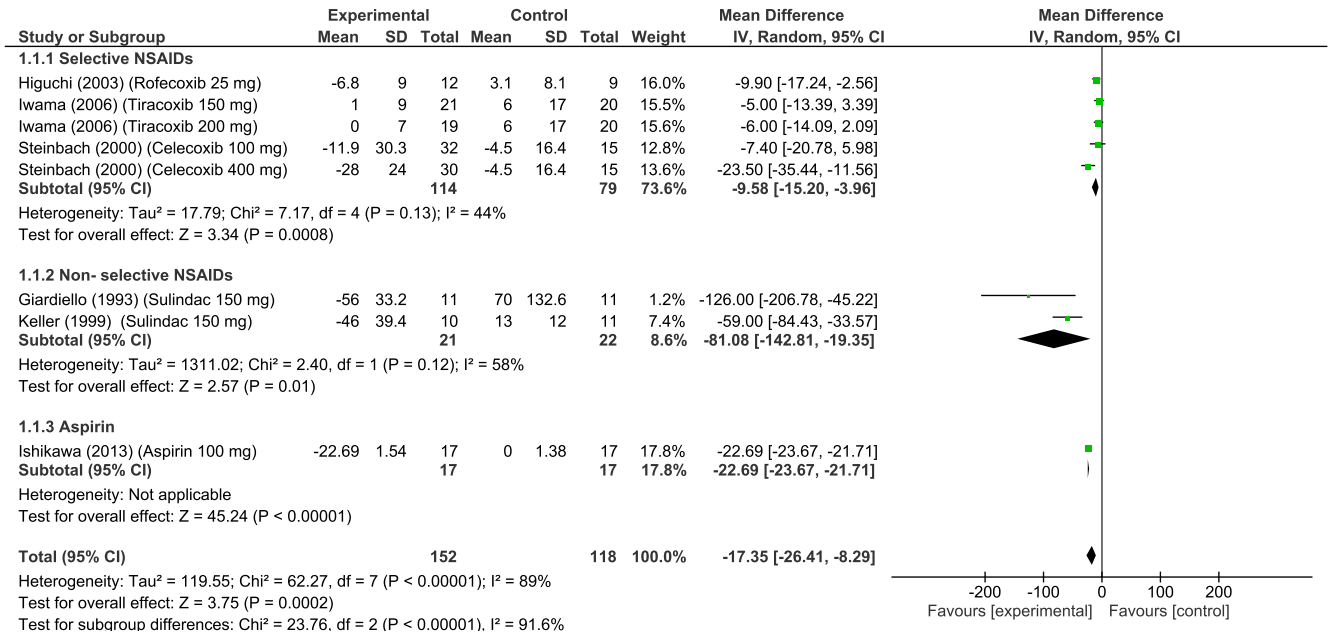

Figure 2. Effect of NSAIDs on polyp number. NSAIDs, nonsteroidal anti-inflammatory drugs.

and issues with RoB) (Figures 2 and 3). In addition, the type of NSAIDs explained inconsistency or heterogeneity between the included studies for polyp number but not for polyp size. For this reason, we downgraded for inconsistency in polyp size only.

Subgroup analysis based on medication type showed the following: the reduction in polyp number and polyp size were highest in patients treated with nonselective NSAIDs: −81.08% (95% CI −142.81%, −19.35%) (I^2 58%), and −75.00% (95% CI −101.36%, 48.64%) (I^2, not applicable), respectively. In patients treated with aspirin, the reduction in polyp number and size was −22.69% (95% CI −23.67%, −21.71%) (I^2, not applicable), and −13.56% (95% CI −14.10%, −13.02%) (I^2 not applicable), respectively. The reduction in polyp number and size was lowest in patients treated with selective NSAIDs −9.58% (95% CI −15.20%, −3.96%) (I^2 44%) and −10.36% (95% CI −20.24%, −0.49%) (I^2 70%).

Only 4 of 8 studies reported gastrointestinal tract-related adverse events.[10–12,28] The most common gastrointestinal adverse events reported were stomatitis, diarrhea, and abdominal pain. We summarized the number of events for the most common gastrointestinal adverse events in Table 2. Gastrointestinal side effects were seen in 13%–33% in the placebo group and 3%–73% in the treatment group. Adverse events that led to drug discontinuation included gastroenteritis and drug allergy. There were no deaths among patients who received NSAIDs. Two studies performed a follow-up esophagogastroduodenoscopy, and no gastric or duodenal mucosal ulcerations were reported.[10,11]

Durability of response of colorectal polyps to NSAIDs

The durability of the response was examined in 2 studies included in our meta-analysis. Giardiello et al reported qualitative data that indicated that 3 months after treatment (treatment duration: 9 months), the number and size of polyps had increased but were still below pretreatment levels.[26] Similarly, Higuchi et al qualitatively described a relapse in rectal polyp number 3 months after completing 9 months of therapy.[11]

Effects on duodenal polyps

We could not quantitatively report on the effects of NSAIDs on the burden of duodenal polyps because only one study fulfilled the inclusion criteria without providing quantitative data. Nugent et al videotaped duodenal polyps in 24 patients (12 treatment, 12 placebo) before and after 6 months of sulindac 200 milligrams taken twice daily and reported that the duodenal polyp burden improved in 5/12 (42%) patients.[30]

Discussion

In this meta-analysis, very low-certainty evidence showed that treatment with NSAIDs for ∼ 6 months reduced the polyp number and size in patients with FAP. Individual studies reported a variable benefit of 12%–77% on polyp numbers and 15%–50%[10,31] on polyp size; some studies did not report any benefit.[32,33] We found that overall, NSAIDs reduced polyp numbers by ∼17% and polyp size by ∼16%. The pooled effects, even though favorable, appear small, but inconsistencies (different bowel preparation methods used, interobserver variability in counting polyps across studies) in reporting the baseline polyp burden may have affected precise estimates and need to be addressed in well-designed future RCTs.

In this meta-analysis, we addressed the limitations of prior meta-analyses on this topic, which were limited by a

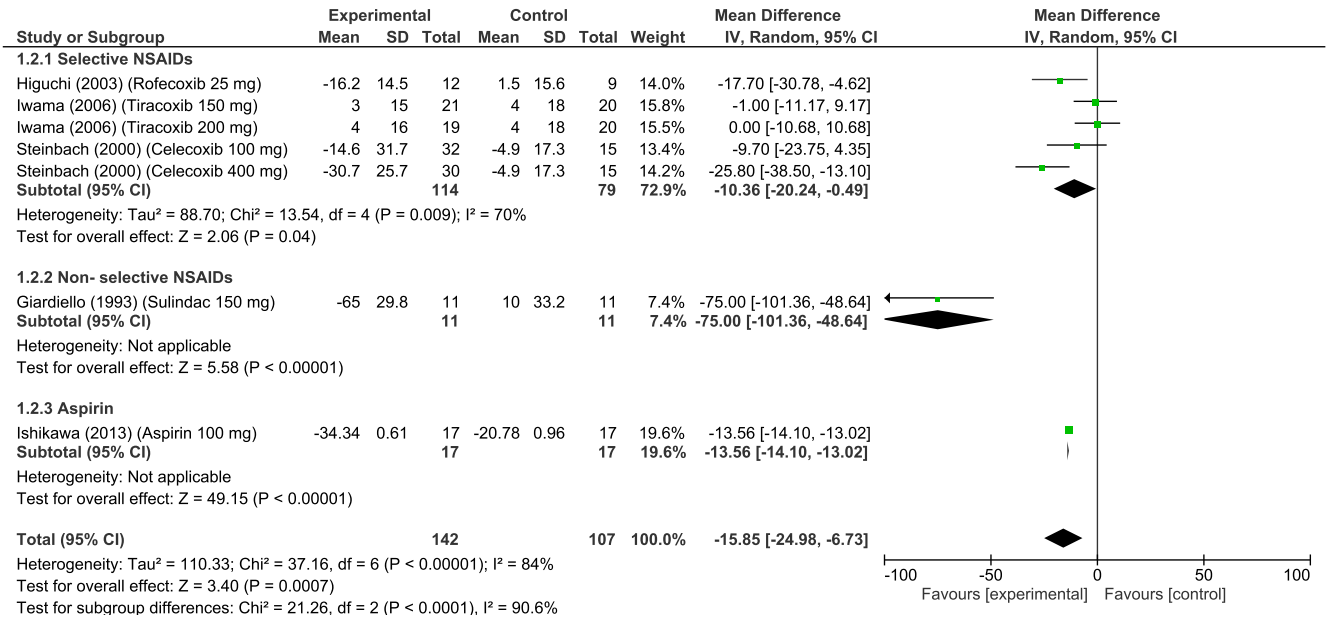

Figure 3. Effect of NSAIDs on polyp size. NSAIDs, nonsteroidal anti-inflammatory drugs.

mixture of RCTs and non-RCTs, did not systematically report bias, and included non-FAP patients.[18,34,35] Cooper et al comprehensively reviewed the RCTs on chemoprevention in FAP patients, but with nonquantitative reporting.[36] None of the prior studies teased out the differences between selective and nonselective NSAIDs.

Although the results showed more reduction in the polyp burden when nonselective NSAIDs and aspirin were used, the number of trials with these agents was small. The largest number of placebo-controlled trials (inclusion criteria for our meta-analysis) tested selective NSAIDs. These limited data may suggest the superiority of nonselective NSAIDs, but the results are far from conclusive due to the high RoB and low certainty of evidence. One could argue that a well-designed and appropriately powered trial to test NSAIDs against a placebo has yet to be done. Given that some newer agents, such as erlotinib, have unacceptable clinical toxicity in patients with FAP,[37] our results suggest that these "older" agents, such as NSAIDs, should be retested by conducting well-designed trials in patients with FAP for prevention of colorectal polyps.

In FAP chemoprevention trials, there are problems with using the polyp number and size as endpoints because of inherent difficulties in counting the polyps and estimating their size during colonoscopy. Clinical outcomes of the need for surgery or therapeutic endoscopic interventions may be better endpoints and were studied in the first-ever chemoprevention trial of 3 active arms (sulindac, eflornithine, and sulindac + eflornithine) in patients with FAP.[38] Polyp number and size are important to the pathogenesis of this disease, but they should be combined with clinical outcomes to provide greater confidence in the results of such trials.

Another important question is the durability of the response to NSAIDs. FAP can present at a young age and thus may require long-term use of NSAIDs, exposing patients to various toxicities, both gastrointestinal and non-gastrointestinal. The current clinical approach is to use NSAIDs to delay the need for surgery in young persons with FAP. If the treatment could delay surgery by several years, it could provide time for personal and professional commitments. Two studies in our meta-analysis provided data about the durability of response. Giardiello et al showed that 3 months after the end of treatment, the number and size of polyps increased compared to nadir but were still lower than the pretreatment numbers.[26] Similarly, Higuchi et al showed that rectal polyps—the authors did not evaluate colon polyps—relapsed 3 months after the end of treatment.[11] These studies suggest that continuous sulindac treatment is needed for polyp suppression, which is supported by other published data. In a long-term follow-up study, the investigators showed that 86% of FAP patients (with only residual rectum) treated continuously with sulindac were polyp-free after a mean follow-up of 63.4 ± 31.3 months.[39]

There were insufficient data to evaluate the effects of NSAIDs on duodenal polyps, which are another major source of morbidity in patients with FAP. One trial qualitatively showed a 42% improvement in the burden of duodenal polyps raising the possibility of an effect.[30] Recent studies have created doubts about the possible benefits of NSAIDs on duodenal polyps. In previous trials, erlotinib alone or in combination with sulindac reduced the duodenal polyp burden in FAP by ~30%.[37,40] The efficacy of NSAIDs on duodenal polyps in FAP needs further evaluation.

Our systematic review has a few limitations. We included only placebo-controlled trials. Therefore, important trials that did not have a placebo arm were excluded,[38] but we wanted to report on the true effect sizes of NSAIDs. We could not systematically report on the durability of

Table 2. Number of Gastrointestinal Adverse Events Reported in the Studies

Adverse events/Study[a]	Any decrease in hemoglobin		Dyspepsia		Diarrhea		Abdominal pain	
	N events (intervention group)	Number of events in placebo group	Number of events in intervention	Number of events in placebo group	Number of events in intervention	Number of events in placebo group	Number of events in intervention	Number of events in placebo group
Iwama et al (2006)[12]	5	0	6	1	14	4	NR	NR
Higuchi et al (2003)[11]	NR	NR	NR	NR	1	0	NR	NR
Steinbach et al (2000)[10]	NR	NR	1	0	10	2	3	2
Ishikawa et al, 2013[28]	1	0	NR	NR	NR	NR	1	NR

NR, not reported.
[a]Only those studies mentioned in the table which reported any gastrointestinal adverse events.

response to treatment because the majority of trials did not provide this information. Finally, inconsistencies in side-effect reporting in the included studies prevented us from quantitatively reporting on the patient tolerance of NSAIDs in this population, but we summarized the adverse event profile in various studies in Table 2. With the development of the National Cancer Institute's Common Terminology Criteria for Adverse Events to report adverse events, capturing the tolerability of the study agent should be less of a concern in future studies.[41] All included studies reported short-term use of NSAIDs (6.4 $\pm$ 2.2 months). Side effects such as kidney disease and peptic ulceration should be considered during the long-term use of NSAIDs for chemoprevention. Another limitation is the heterogeneity between studies due to multiple factors, including the year of study with regard to endoscopic developments, sex differences, medication adherence, limitations of measurements of polyp number and size, and variability in genetic confirmation of FAP. We examined possible reasons for heterogeneity by performing select subgroup analyses, which did numerically reduce I^2 for some analyses, but the overall heterogeneity persisted as reflected in the GRADE assessments that varied from low to very low certainty of evidence. The results of all subgroup analyses, especially post hoc analyses, should be interpreted cautiously because of the risk of identifying spurious subgroup effects. Future well-designed studies are urgently needed to understand the true effect sizes of NSAIDs on polyp burden in FAP.

Conclusion

We report a rigorous systematic review and meta-analysis of RCTs of selective and nonselective NSAIDs in patients with FAP and analyze clinical efficacy (both the polyp number and size) and safety. However, our conclusions were hampered by inconsistent methodology in prior studies and highlighted the need for increased rigor in future studies. In addition, although NSAIDs may have an effect on this difficult-to-manage disease, more data are needed before NSAIDs can be universally recommended for chemoprevention.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2023.05.009.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
The data, analytic methods, and study materials will not be made available to other researchers.

Reporting Guidelines:
PRISMA, CONSORT.