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

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Background: Celecoxib has previously been shown to be effective in reducing recurrent colorectal adenomas, but its long-term effects are unknown. In addition, safety issues are of major concern. Therefore, we examined the efficacy and safety of celecoxib as a chemopreventive agent along with its posttreatment effect.

Methods: We performed a meta-analysis based on a systematic review of randomized controlled trials (RCTs) comparing celecoxib at various doses (400 mg once daily, 200 mg twice daily, and 400 mg twice daily) vs placebo in persons with history of colorectal adenomas. Several databases were searched from inception up to April 2018. Long-term follow-ups of RCTs were also included to evaluate posttreatment effect. Primary outcome was the incidence of recurrent colorectal adenomas. Various safety outcomes were evaluated, especially cardiovascular (CV) events. Risk–benefit integrated analyses were also performed.

Results: A total of three RCTs (4,420 patients) and three post-trial studies (2,159 patients) were included in the analysis. Use of celecoxib at any dose for 1–3 years significantly reduced the incidence of recurrent advanced adenomas (risk ratio, 0.42 [95% CI, 0.34–0.53]) and any adenomas (0.67 [95% CI, 0.62–0.72]) compared with placebo. Subgroup analysis on different dosing suggested a greater effect with 400 mg twice daily. However, celecoxib 400 mg twice daily significantly increased the risk of serious adverse (1.2 [95% CI, 1.0–1.5]) and CV events (3.42 [95% CI, 1.56–7.46]), while celecoxib at 400 mg/day, especially with once daily dosing, did not increase CV risk (1.01 [95% CI, 0.70–1.46]). Analysis of post-trial studies indicated that the treatment effect disappeared (1.15 [95% CI, 0.88–1.49]) after discontinuing celecoxib for >2 years.

Conclusion: Celecoxib 400 mg once daily dosing could potentially be considered as a viable chemopreventive option in patients with high risk of adenomas but with low CV risk. Long-term trials on celecoxib at a dose of ≤400 mg either once or twice daily are warranted.

Keywords: colorectal cancer, colorectal adenomas, chemoprevention, celecoxib, meta-analysis, randomized controlled trials, risk–benefit integrated analyses

Background

Colorectal cancer (CRC) is the third most common cancer worldwide, with over 1.4 million new cases estimated to have occurred in 2012.1 It is widely accepted that adenomas/polyps are well-known precursors of sporadic CRCs.2 Early detection and removal of adenomatous polyps by colonoscopic screening has been showed to reduce mortality from CRC.3 Unfortunately, surveillance colonoscopic screening is underutilized.4–6 A variety of reasons, including suboptimal adherence to screening, availability, and cost, may play a part in this problem. For those who undergo polypectomy, the...
reurrence rate is still relatively high. Therefore, the use of chemoprevention strategies to complement surveillance screening may have a potential to further reduce CRC morbidity and mortality among those with adenomatous polyps.

Protective effect of non-aspirin nonsteroidal antiinflammatory drugs (NSAIDs) on colorectal adenomas have been documented in previous systematic reviews. However, concerns about cardiovascular (CV) safety and risk of serious bleeding events hamper the acceptance of these strategies for secondary prevention of CRC. Cyclooxygenase-2 (COX-2) inhibitors selectively interfere with COX-2 enzyme and have been shown to cause less major bleeding compared with traditional NSAIDs. For CV safety, most non-aspirin NSAIDs and COX-2 inhibitors have been shown to increase the risk of thrombotic CV events. However, the risk of these events may be a result of complex interplay among a specific drug molecule, dose, and baseline CV risk. Rofecoxib, which was withdrawn from the market, was shown to have a much higher risk compared with celecoxib. For celecoxib, the risk appeared to be dose dependent and was evident among patients with high CV risk at baseline. In addition, available evidence suggested that twice daily dosing, not once daily dosing, was associated with increased CV risk. Recently, celecoxib at approved doses (200–400 mg/day), was found to be noninferior to ibuprofen or naproxen with regard to CV safety in a large, randomized, controlled trial with over 24,000 patients. As a result, celecoxib at approved doses could be a viable option for patients with history of adenomas where the risk of CRC may outweigh the risk of CV events. We, therefore, conducted a systematic review and meta-analysis to evaluate efficacy and safety of celecoxib in patients with a history of adenomas. We performed risk–benefit integrated analysis to comprehensively evaluate celecoxib’s multidimensional effects in this setting. Moreover, we also investigated whether the adenoma-preventive effect of celecoxib waned after withdrawal.

Methods
Study design
This study was performed as part of a systematic review that has been previously registered (PROSPERO CRD42015025849) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Search strategy and study selection
We identified relevant studies through a systematic search of Medline and EMBASE until April 2018. In addition, we searched published systematic reviews for additional studies. The search strategy is provided in Table S1. Studies included were randomized controlled trials (RCTs) and long-term follow-up of RCTs that met the following inclusion criteria: participants were adults (aged ≥18 years) at an increased risk due to a previous history of adenomas who underwent polypectomy and with a documented clean colon before randomization; intervention was celecoxib at any dose; the comparator was placebo or control; and the outcome was the proportion of subjects who developed colorectal neoplasia, described as either colorectal adenomas or advanced adenomas.

Outcomes of interest
Primary efficacy outcomes of interest were the incidence of recurrent colorectal adenomas (advanced adenomas and any adenomas). Advanced adenoma was defined by one or more of the following features: 1 cm or larger, with villous or tubulovillous histology, with high-grade dysplasia, and/or with intramuscosal carcinoma or invasive cancer. Any adenomas include both advanced and nonadvanced adenomas (defined as one or two small [≤1 cm] tubular adenomas or serrated polyps without cytologic dysplasia) and invasive cancers.

Safety outcomes were the incidence of CRC, mortality due to any causes, serious adverse events, serious CV events, and renal and hypertensive disorders reported on any follow-up after randomization. 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. Serious CV events were defined as the composite of CV death, myocardial infarction, stroke, heart failure, thromboembolic event, or defined as serious CV event by the study investigators. Renal and hypertensive disorders included reports of elevated serum creatinine levels, fluid retention and edema, hypertension, proteinuria, and renal failure. We also evaluated the posttreatment effects of celecoxib on the incidence of recurrent colorectal neoplasia after discontinuing the intervention for >2 years.

Data extraction and quality assessment
Two reviewers (SKV and KGL) screened the relevant publications and then extracted data on the study, participants, and treatment-related characteristics onto a standardized form, and discrepancies were resolved by another author after group discussion. Data on efficacy outcomes were extracted with modified intention-to-treat analysis (ie, subjects who received at least one dose of celecoxib at any dose and had
at least one colonoscopy after randomization). Data on safety outcomes were extracted by intention-to-treat principle, using the initial number of randomized participants allocated to each trial arm. Participants who were lost to follow-up were considered free of adverse events.

Previous evidence suggested that the effects of NSAIDs on adenoma recurrence may not be sustained after treatment cessation.30–32 Hence, we abstracted efficacy outcomes measured cumulatively at two time points, within 1 year of discontinuing intervention (primary efficacy analysis) and ≥2 years after discontinuing intervention (posttreatment effect analysis). Two reviewers (SKV and SMC) independently assessed the risk of bias (ROB) in the context of the primary outcome by using the revised Cochrane risk of bias tool (RoB 2.0).33

Data synthesis and statistical analysis
Meta-analysis was performed with DerSimonian and Laird random-effects model to estimate pooled risk ratios and 95% confidence intervals incorporating heterogeneity within and between studies, with Stata version 14.0 (StataCorp, College Station, TX, USA).34 Statistical heterogeneity between trials was assessed for primary outcomes using I2 statistics, with values ≥50% indicating substantial levels of heterogeneity.35,36 Publication bias could not be assessed due to the small number of included studies, which limited the power to distinguish between finding by chance and real asymmetry.37 Subgroup analyses were performed for different dosings of celecoxib38 including 200 mg twice daily (400 mg/day), 400 mg once daily, and 400 mg twice daily (800 mg/day). Sensitivity analyses were performed based on the use of surveillance colonoscopy per protocol completer analysis (outcomes included only those subjects who underwent colonoscopy surveillance at the prespecified time period per protocol and excluded subjects who underwent a colonoscopic surveillance assessment before the expected surveillance interval), fixed-effect model, and trials with low ROB.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence (high, moderate, low, and very low) of estimates derived from meta-analyses using GRADEpro version 3.6.1 (McMaster University, 2014).39

Results
Study selection
We identified 391 records in which 11 potentially eligible articles were reviewed in full text. Of these, six articles were excluded mostly due to the lack of eligible population. Therefore, a total of five studies were included in our review. Among these five studies, three trials23,24,41 met the eligibility criteria for the quantitative analysis of primary outcomes. Post-trial results from three studies20,31,41 were included for the analysis of posttreatment effect on the incidence of recurrent adenomas. The PRISMA flow diagram depicting the search and selection process for the primary outcomes is displayed in Figure S1.

Characteristics of the included studies
Table 1 describes the characteristics of three RCTs23,24,41 which reported the incidence of recurrent colorectal adenomas. A total of 4,420 participants with a previous history of adenomas who underwent polypectomy and with documented clean colon before randomization were included in the analysis. All trials were double-blinded and placebo-controlled. The treatment duration was 3 years in two trials23,24 and 1 year in one trial.41 Postrandomization colonoscopy was performed within 1 year of discontinuing intervention in all trials. The dose per day of celecoxib used in two trials was 400 mg once daily,23,41 and the remaining trial24 tested both 400 mg (200 mg twice daily) and 800 mg (400 mg twice daily) doses. A
<table>
<thead>
<tr>
<th>Reference year</th>
<th>Study name</th>
<th>Design</th>
<th>Treatment duration (years)</th>
<th>Follow-up colonoscopy</th>
<th>Subjects (n originally randomized)</th>
<th>Study group</th>
<th>Efficacy outcomes (n/N)</th>
<th>Safety outcomes (n/N)</th>
<th>High CV risk, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>PreSAP</td>
<td>Multicenter, double-blind, placebo-controlled, RCT, parallel two-arm</td>
<td>3</td>
<td>At year 1, year 3, or both</td>
<td>Median age 61; 66% males</td>
<td>Celecoxib 400 mg once daily (n=933)</td>
<td>42/840</td>
<td>270/840</td>
<td>6/933</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo (n=628)</td>
<td>56/557</td>
<td>264/557</td>
<td>1/628</td>
</tr>
<tr>
<td>2006</td>
<td>APC</td>
<td>Multicenter, double-blind, placebo-controlled, RCT, parallel three-arm</td>
<td>3</td>
<td>At year 1, year 3, or both</td>
<td>Median age 59; 68% males</td>
<td>Celecoxib 200 mg twice daily (n=685)</td>
<td>44/613</td>
<td>252/613</td>
<td>0/685</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Celecoxib 400 mg twice daily (n=671)</td>
<td>35/601</td>
<td>213/601</td>
<td>4/671</td>
</tr>
<tr>
<td>2016</td>
<td>Sel/Cel</td>
<td>Multicenter, double-blind, placebo-controlled, RCT, 2x2 factorial</td>
<td>1a</td>
<td>Within 1 year of discontinuing intervention</td>
<td>Mean age 63; 68% males</td>
<td>Celecoxib 400 mg once daily (n=414)</td>
<td>3/119</td>
<td>34/123</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo (n=410)</td>
<td>12/119</td>
<td>50/121</td>
<td>NA</td>
</tr>
</tbody>
</table>

Notes: aAdjudicated data from Solomon et al.; bStudy reported the median time for taking placebo and intervention, respectively, was 13.6 and 14.2 months; cEfficacy outcomes at different time intervals were reported after discontinuing intervention; as per our protocol, we have used data from subjects undergoing colonoscopy within 1 year of discontinuing intervention; dAdvanced status uncertain for six participants; n= number of events; N= number of participants.

Abbreviations: APC, Adenoma Prevention with Celecoxib trial; CRC, colorectal cancer; CV, cardiovascular; PreSAP, Prevention of Colorectal Sporadic Adenomatous Polyps Study; RCT, randomized controlled trial; Sel/Cel, Selenium and Celecoxib (Sel/Cel) Trial; NA, not available.
detailed description of ROB assessment among included RCTs is presented in Table S2. Among three RCTs, one trial was judged to be at high ROB and the remaining two trials were judged to be at low ROB in all domains.

Post-trial results from three studies were available to investigate the effect of celecoxib withdrawal on incidence of recurrent colorectal adenomas. Table 2 describes the identified studies. A total of 2,159 participants who completed follow-up colonoscopy after discontinuing intervention for 2–4 years were included in the analysis.

Effects on the primary efficacy outcomes
Based on the results from the meta-analyses, use of celecoxib at any dose (400–800 mg/day) for a duration of approximately 1–3 years showed a statistically significant reduction in the recurrence of advanced colorectal adenomas (RR, 0.42 [95% CI, 0.34–0.53]) and any adenomas (RR, 0.67 [95% CI, 0.62–0.72]) compared with placebo, with no heterogeneity (I²=0%; Figure 1). In the sensitivity analyses, findings were robust and consistent with the primary analysis. A subgroup analysis of celecoxib at 400 mg/day demonstrated similar effects on advanced adenomas (RR, 0.45 [95% CI, 0.35–0.58]) and any adenomas (RR, 0.69 [95% CI, 0.64–0.75]), with no heterogeneity (I²=0%; Figure 1). Both 400 mg once daily and 200 mg twice daily dosing regimens provided similar effect size (Figure S5).

For celecoxib at 800 mg/day, RR for advanced adenomas was 0.34 [95% CI, 0.24–0.50] and 0.55 [95% CI, 0.48–0.64] for any adenomas.

Effects on the safety outcomes
Results from meta-analyses (Figure 2) showed that celecoxib at any dose for a duration of approximately 1–3 years significantly increases the risk of serious adverse events (RR, 1.15 [95% CI, 1.02–1.30]) and renal-hypertensive disorders (RR, 1.25 [95% CI, 1.09–1.42]) compared with placebo. Other safety outcomes including serious CV events (RR, 1.44 [95% CI, 0.73–2.84]), all-cause mortality (RR, 1.27 [95% CI, 0.66–2.44]), and CRCs (RR, 1.41 [95% CI, 0.24–8.27]) were not significantly increased compared to placebo. Subgroup analysis based on different dosing regimens showed that celecoxib 400 mg twice daily (800 mg/day) significantly increased the risk of serious adverse (RR, 1.2 [95% CI, 1.0–1.5]) and CV events (RR, 3.42 [95% CI, 1.56–7.46]). Interestingly, for celecoxib at 400 mg/day, a significant increase in CV risk was observed only with 200 mg twice daily regimen (RR, 2.48 [95% CI, 1.10–5.59]) but not with 400 mg once daily regimen (RR, 1.01 [95% CI, 0.70–1.46]), compared with placebo (Figures S6 and S7).

Table 2: Studies reporting posttreatment effect of celecoxib on incidence of recurrent colorectal adenomas after 2 years of off-treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>Subjects completed follow-up colonoscopy, n</th>
<th>Study group (N, originally randomized)</th>
<th>Duration of off-treatment (years)</th>
<th>Treatment duration (years)</th>
<th>Efficacy outcomesa</th>
<th>Advanced adenomas</th>
<th>Any adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arber et al, 2011b</td>
<td>Follow-up of double-blind, placebo-controlled RCT; multicenter; parallel two-arm</td>
<td>Celecoxib 400 mg/day (n=685) and placebo (n=628)</td>
<td>5 2</td>
<td>Celecoxib 400 mg/day (n=685) and placebo (n=628)</td>
<td>3 5 2</td>
<td>Celecoxib 400 mg/day (n=685) and placebo (n=628)</td>
<td>3 5 2</td>
<td>Celecoxib 400 mg/day (n=685) and placebo (n=628)</td>
<td>3 5 2</td>
</tr>
<tr>
<td>Bertagnolli et al, 2009</td>
<td>Follow-up of double-blind, placebo-controlled RCT; multicenter; parallel three-arm</td>
<td>Celecoxib 800 mg/day (n=792) and placebo (n=772)</td>
<td>5 5</td>
<td>Celecoxib 800 mg/day (n=792) and placebo (n=772)</td>
<td>3 5 2</td>
<td>Celecoxib 800 mg/day (n=792) and placebo (n=772)</td>
<td>3 5 2</td>
<td>Celecoxib 800 mg/day (n=792) and placebo (n=772)</td>
<td>3 5 2</td>
</tr>
<tr>
<td>Thompson et al, 2016c</td>
<td>Follow-up of double-blind, placebo-controlled RCT; multicenter</td>
<td>Celecoxib 400 mg/day (n=124) and placebo (n=124)</td>
<td>5 5</td>
<td>Celecoxib 400 mg/day (n=124) and placebo (n=124)</td>
<td>3 5 2</td>
<td>Celecoxib 400 mg/day (n=124) and placebo (n=124)</td>
<td>3 5 2</td>
<td>Celecoxib 400 mg/day (n=124) and placebo (n=124)</td>
<td>3 5 2</td>
</tr>
</tbody>
</table>

**Notes:**
- efficacy outcomes from 639 subjects with a follow-up colonoscopy within 3.5 years of qualifying colonoscopy. Study reported efficacy outcomes from follow-up colonoscopy within 5.5 years. Number of advanced adenomas uncertain for some participants.
- Abbreviations: APC, Adenoma Prevention with Celecoxib trial; PreSAP, Prevention of Colorectal Sporadic Adenomatous Polyposis Study; RCTs, randomized controlled trials; Sel/Cel, Selenium and Celecoxib (Sel/Cel) Trial; NA, not available.
Grade summary of evidence

Our application of GRADE methodology led us to conclude that the accumulated evidence for celecoxib (at any dose and 400 mg/day) is of high quality for adenoma prevention. Detailed information on GRADE summary of evidence is presented in Table S3.

Risk–benefit integrated analysis

Based on integrated analysis, we estimated that the use of celecoxib at 800 mg/day compared with placebo may lead to 108 (95% CI, 82–124) and 49 (95% CI, 30–56) fewer advanced adenomas in 1,000 patients with high-risk and low-risk adenomas, respectively. On the other hand, this would lead to an excess of 38 (95% CI, 0–95) serious adverse events and 82 (95% CI, 19–186) CV events compared with placebo. As for celecoxib at 400 mg/day, there would be 90 (95% CI, 68–106) and 41 (95% CI, 32–48) fewer advanced adenomas in persons with high-risk and low-risk adenomas, respectively. As for harm, this intervention would lead to an excess of 25 (95% CI, 2 fewer to 53 more) serious adverse events and 11 (95% CI, 8 fewer to 44 more) CV events, per 1,000 patients treated compared with placebo. The risk–benefit balance may also be different when different dosing regimens of 400 mg/day are used. Interestingly, celecoxib at 400 mg once daily may be associated with less harm since this dosing regimen would only lead to 30 excess harm-

Study | RR (95% CI) | Events, treatment | Events, control | % weight |
--- | --- | --- | --- | --- |
(a) Celecoxib at any dose: advanced adenomas
PreSAP | 0.50 (0.34, 0.73) | 42/840 | 56/557 | 33.30 |
APC | 0.40 (0.30, 0.53) | 79/1214 | 99/608 | 63.48 |
Sel/Cel | 0.25 (0.07, 0.86) | 3/119 | 12/119 | 3.22 |
Subtotal (I²=0.0%, P=0.466) | 0.42 (0.34, 0.53) | 124/2173 | 167/1284 | 100.00 |
(b) Celecoxib at any dose: any adenomas
PreSAP | 0.68 (0.59, 0.77) | 270/840 | 264/557 | 34.09 |
APC | 0.66 (0.60, 0.73) | 465/1214 | 354/608 | 61.26 |
Sel/Cel | 0.67 (0.47, 0.96) | 34/123 | 50/121 | 4.65 |
Subtotal (I²=0.0%, P=0.935) | 0.67 (0.62, 0.72) | 769/2177 | 668/1286 | 100.00 |
(c) Celecoxib 400 mg/day: advanced adenomas
PreSAP | 0.50 (0.34, 0.73) | 42/840 | 56/557 | 41.57 |
APC | 0.44 (0.31, 0.62) | 44/613 | 99/608 | 54.41 |
Sel/Cel | 0.25 (0.07, 0.86) | 3/119 | 12/119 | 4.02 |
Subtotal (I²=0.0%, P=0.566) | 0.45 (0.35, 0.58) | 89/1572 | 167/1284 | 100.00 |
(d) Celecoxib 400 mg/day: any adenomas
PreSAP | 0.68 (0.59, 0.77) | 270/840 | 264/557 | 41.36 |
APC | 0.71 (0.63, 0.79) | 252/613 | 354/608 | 52.99 |
Sel/Cel | 0.67 (0.47, 0.96) | 34/123 | 50/121 | 5.64 |
Subtotal (I²=0.0%, P=0.886) | 0.69 (0.64, 0.75) | 556/1576 | 668/1286 | 100.00 |

Figure 1 Effects on the primary efficacy outcomes.
Notes: Efficacy outcomes measured cumulatively from baseline, on postrandomization colonoscopy performed within 1 year of discontinuing intervention. Celecoxib at any dose: 400–800 mg/day.
Abbreviations: APC, Adenoma Prevention with Celecoxib trial; PreSAP, Prevention of Colorectal Sporadic Adenomatous Polyposis study; Sel/Cel, Selenium and Celecoxib (Sel/Cel) Trial.
ful events (29 serious adverse events and one CV event) compared with 65 events (15 serious adverse events and 50 CV events) with 200 mg twice daily regimen. Based on this analysis, the risk–benefit balance of celecoxib at 400 mg/day, especially with 400 mg once daily dosing may be acceptable especially among patients at high risk of CRC and at low CV risk (Table S4).

Posttreatment effect on efficacy outcomes

Meta-analyses of post-trial studies demonstrated no effect on the recurrence of advanced colorectal adenomas (RR, 1.15 [95% CI, 0.67–1.99]) and any adenomas (RR, 1.15 [95% CI, 0.88–1.49]) after discontinuing celecoxib for more than 2 years (Figure S8). There was moderate to substantial level of heterogeneity observed in both analyses.

Discussion

Previous meta-analyses suggested a substantial protective effect of non-aspirin NSAIDs on colorectal adenoma recurrence. Although the exact mechanism of action remains to be elucidated, both COX-dependent and COX-independent mechanisms have been shown to contribute to the antitumor effects. Despite such promising data, use of long-term NSAIDs for cancer prevention is not very well received due to their significant toxicity, especially CV toxicity. However, CV toxicity of NSAIDs is a complicated phenomenon, which is a result of a complex interplay mainly between baseline

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**Figure 2** Effects of celecoxib at any dose on the safety outcomes.

**Abbreviations:** APC, Adenoma Prevention with Celecoxib trial; CRC, colorectal cancer; CV, cardiovascular; PreSAP, Prevention of Colorectal Sporadic Adenomatous Polyps Study; Sel/Cel, Selenium and Celecoxib (Sel/Cel) Trial.

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<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Events, treatment</th>
<th>Events, control</th>
<th>% weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreSAP</td>
<td>1.18 (0.95, 1.47)</td>
<td>186/933</td>
<td>106/628</td>
<td>32.04</td>
</tr>
<tr>
<td>APC</td>
<td>1.16 (0.96, 1.39)</td>
<td>293/1356</td>
<td>127/679</td>
<td>42.87</td>
</tr>
<tr>
<td>Sel/Cel</td>
<td>1.11 (0.87, 1.41)</td>
<td>104/414</td>
<td>93/410</td>
<td>25.09</td>
</tr>
<tr>
<td>Subtotal (I²=0.0%, P=0.927)</td>
<td>1.15 (1.02, 1.30)</td>
<td>583/2703</td>
<td>326/1717</td>
<td>100.00</td>
</tr>
<tr>
<td>Serious CV events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreSAP</td>
<td>1.29 (0.65, 2.57)</td>
<td>23/933</td>
<td>12/628</td>
<td>31.34</td>
</tr>
<tr>
<td>APC</td>
<td>2.94 (1.40, 6.19)</td>
<td>47/1356</td>
<td>8/679</td>
<td>29.79</td>
</tr>
<tr>
<td>Sel/Cel</td>
<td>0.91 (0.59, 1.41)</td>
<td>35/414</td>
<td>38/410</td>
<td>38.86</td>
</tr>
<tr>
<td>Subtotal (I²=72.5%, P=0.026)</td>
<td>1.44 (0.73, 2.84)</td>
<td>105/2703</td>
<td>58/1717</td>
<td>100.00</td>
</tr>
<tr>
<td>Mortality (any causes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreSAP</td>
<td>1.06 (0.41, 2.71)</td>
<td>11/933</td>
<td>7/628</td>
<td>48.77</td>
</tr>
<tr>
<td>APC</td>
<td>1.50 (0.60, 3.77)</td>
<td>18/1356</td>
<td>6/679</td>
<td>51.23</td>
</tr>
<tr>
<td>Subtotal (I²=0.0%, P=0.601)</td>
<td>1.27 (0.66, 2.44)</td>
<td>29/2289</td>
<td>13/1307</td>
<td>100.00</td>
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<tr>
<td>Renal/hypertensive disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreSAP</td>
<td>1.35 (1.08, 1.69)</td>
<td>193/933</td>
<td>96/628</td>
<td>35.34</td>
</tr>
<tr>
<td>APC</td>
<td>1.17 (0.98, 1.41)</td>
<td>305/1356</td>
<td>130/679</td>
<td>52.17</td>
</tr>
<tr>
<td>Sel/Cel</td>
<td>1.27 (0.87, 1.84)</td>
<td>55/414</td>
<td>43/410</td>
<td>12.49</td>
</tr>
<tr>
<td>Subtotal (I²=0.0%, P=0.626)</td>
<td>1.25 (1.09, 1.42)</td>
<td>553/2703</td>
<td>269/1717</td>
<td>100.00</td>
</tr>
<tr>
<td>CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreSAP</td>
<td>4.04 (0.49, 33.46)</td>
<td>6/933</td>
<td>1/628</td>
<td>41.36</td>
</tr>
<tr>
<td>APC</td>
<td>0.67 (0.15, 2.97)</td>
<td>4/1356</td>
<td>3/679</td>
<td>58.64</td>
</tr>
<tr>
<td>Subtotal (I²=48.3%, P=0.164)</td>
<td>1.41 (0.24, 8.27)</td>
<td>10/2289</td>
<td>4/1307</td>
<td>100.00</td>
</tr>
</tbody>
</table>
CV risk and the nature of each NSAID along with its dose. Celecoxib, a selective COX-2 inhibitor, is among a few NSAIDs that have been tested in a number of studies for CRC prevention. Although its efficacy in this indication looked initially promising, CV toxicity shown from cancer prevention trials thwarted the interest of the medical community.

Nevertheless, a previous review has suggested that moderate dose of celecoxib (≤400 mg/day) might not be associated with an increased CV risks. Recently, the PRECISION trial which was a large, randomized, CV safety trial comparing celecoxib at ≤400 mg/day with ibuprofen and naproxen suggested that celecoxib at this dose may not confer unacceptable CV risk along with other serious adverse events. As a result, a comprehensive evaluation to understand the totality of risk–benefit equation, which may vary with different levels of risk. Thus, a clearer picture of an agent with multidimensional effects can be seen.

The results of our study showed that celecoxib demonstrated a dose-dependent effect in the reduction of adenoma recurrence and the risks of serious adverse events during a follow-up of up to 3 years. Our findings on celecoxib are consistent with those from previous meta-analyses regarding the benefits of non-aspirin NSAIDs for the prevention of recurrent adenomas. For risk–benefit balance, we found that benefit of celecoxib at 400 mg/day may outweigh the risks of adverse events in patients with varying risk of adenomas to increase understanding of the risk–benefit equation, which may vary with different levels of risk. Thus, it is very uncertain, adverse effects of celecoxib at these low levels of dosing. This may allow celecoxib to be more acceptable for long-term use if it can be demonstrated to show some efficacy for this indication at this low level of dosing.

The preventive effect of celecoxib, as shown in our analysis, waned after ≥2 years of treatment cessation. The lack of a sustained clinical effect may reflect a rebound of COX-2 expression, or cessation of an alternative mechanism independent of COX-2 inhibition, as described previously. This is consistent with an increased risk of adenomas after 2 years of celecoxib discontinuation in the PreSAP trial, which is similar to the APPROVe study with rofecoxib. These data suggested that celecoxib may need to be employed on a long-term basis. Since both efficacy and adverse events can be cumulative, future study of celecoxib may need to be long term to fully elucidate the true balance on risk and benefit of this agent.
Our study has several important limitations. First, the limited number of trials along with their short duration, some of which were terminated early, may not provide sufficient data to genuinely represent the long-term risk and benefit of celecoxib. Second, by using a pooled estimate of population data from the National Cancer Institute pooling project, our analysis may be limited by the nature of the source data that were derived mainly from a Caucasian population and a specific geographical area. Since significant differences exist among various subtypes of CRC across the world, the applicability of such data to other parts of the world may be limited. This is also the case for pooled estimate on CV events where different rates of CV events are seen among different racial groups and geographical areas. Third, we did not analyze the impact of aspirin use on the risk–benefit of celecoxib. This was due to the fact that we were unable to obtain patient-level data of these included trials. Aspirin could potentially alter the risk–benefit balance of celecoxib if used concomitantly. This is due to the fact that aspirin has a modest protective effect on CRC and CV events, yet possesses gastrointestinal toxicity along with major bleedings. As a result, readers should be aware of this limitation. Lastly, based on these limitations, our data are useful only for hypothesis generation and cannot be considered definitive. Future research on celecoxib as a chemopreventive agent may potentially be considered but must be employed at a dose of ≤400 mg either once or twice daily.

Conclusion
In this comprehensive evaluation with risk–benefit integrated analysis, celecoxib at the dose of ≤400 mg/day could potentially be considered as a viable chemopreventive option, especially with a 400 mg once daily regimen. This may be particularly attractive in patients with high risk of adenomas but with low CV risk. Example of this patient group is a patient who has a history of high-risk adenomas and also has <5% of a 10-year risk of developing atherosclerotic CV disease. Celecoxib at a higher dose should be discouraged due to the unacceptable high level of risk compared with small benefit gained by increasing the dose beyond 400 mg/day. However, more long-term trials on celecoxib at a dose of ≤400 mg either once or twice daily are warranted to fully elucidate the true balance on risk and benefit of this agent.

Transparency declaration
The corresponding authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Data sharing statement
Technical appendix and dataset are available from the corresponding author.

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Disclosure
The authors report no conflicts of interest in this work.

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