



EUROPEAN COMMISSION
JOINT RESEARCH CENTRE
Directorate F – Health and Food (Ispra)
Disease Prevention

European Commission Initiative on Colorectal Cancer (ECICC): European guidelines on colorectal cancer primary prevention, screening and diagnosis

Draft recommendations for public consultation

QUESTION

Should non-aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs, including, preferential COX-2 inhibitors, COX-2 selective inhibitors, other non-selective COX inhibitors) vs. no non-aspirin NSAIDs be used for primary prevention of colorectal cancer in average risk adults?

POPULATION:	Asymptomatic adults at average risk of colorectal cancer
INTERVENTION:	non-aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs, including, preferential COX-2 inhibitors, COX-2 selective inhibitors, other non-selective COX inhibitors)
COMPARISON:	no non-aspirin NSAIDs
MAIN OUTCOMES:	Death from colorectal cancer; Diagnosis of colorectal cancer; Cardiovascular Events; Major gastrointestinal bleeding; Gastrointestinal perforation; Gastrointestinal adverse effects; Gastrointestinal ulcers; Acute kidney injury.
SETTING:	European Union
PERSPECTIVE:	Population (National Health System)
BACKGROUND:	<p>Colorectal cancer is a malignant tumour that forms in the tissues of the colon (the longest part of the large intestine) or of the rectum (the final part of the digestive tract). It is estimated that, in EU-27 countries in 2020, colorectal cancer accounted for 12.7% of all new cancer diagnoses and 12.4% of all deaths due to cancer. That made it the second most frequently occurring cancer (after breast cancer) and the second cause of cancer death (after lung cancer) (JRC, 2021).</p> <p>The use of non-aspirin NSAIDs for CRC prevention remains controversial. Recognizing the need for clearer guidance, the ECICC Working Group (WG) has prioritized this question.</p>
CONFLICT OF INTERESTS:	<p>Conflicts of interest (CoI) for ECICC working group (WG) members and subgroup members were assessed and managed by the European Commission's Joint Research Centre (JRC) following an established procedure in line with institutional rules. Participation in the development of the recommendations was restricted, according to CoI disclosure. Consequently, for this question, no WG or subgroup members were recused from voting.</p> <p>For more information visit: https://healthcare-quality.jrc.ec.europa.eu/en/ecicc/discover-ecicc/working-groups</p>

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know 	<p>The overall colorectal cancer trends are increasing for incidence and decreasing for mortality, but there are national and regional exceptions and large variability among EU-27 countries. National differences can in part be explained by differing levels of healthcare expenditure and the resulting quality of screening, diagnosis, and treatment.</p> <p>Beyond these measures, has been extensively investigated as a strategy to reduce CRC incidence and its precursor lesions. The use of non-aspirin NSAIDs for CRC prevention remains controversial, as its potential benefits must be weighed against the risks of adverse effects.</p>	<p>This healthcare question focused on whether non-aspirin NSAIDs should be used for primary prevention of CRC in asymptomatic average risk adults.</p> <p>The working group (WG) prioritised this question for the ECICC.</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																				
<ul style="list-style-type: none"> ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know 	<p>Date of last search: January 2023</p> <table border="1"> <thead> <tr> <th rowspan="2">Outcomes</th> <th rowspan="2">Nº of participants (studies) Follow-up</th> <th rowspan="2">Certainty of the evidence (GRADE)</th> <th rowspan="2">Relative effect (95% CI)</th> <th colspan="2">Anticipated absolute effects* (95% CI)</th> </tr> <tr> <th>Risk with no non-aspirin NSAIDs</th> <th>Risk difference with non-aspirin NSAIDs (including other non-selective COX inhibitors, preferential COX-2 inhibitors, COX-2 selective inhibitors)</th> </tr> </thead> <tbody> <tr> <td>Death from colorectal cancer (CRC mortality) - not reported</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>Diagnosis of colorectal cancer (CRC incidence) at 10 years follow-up: mean 8.4 years</td> <td>53471 (1 non-randomised study)¹</td> <td>⊕○○○ Very low^{a,b,c,d}</td> <td>HR 0.73 (0.51 to 1.04)</td> <td>Estimated risk at 10-year timeframe 1,080 per 100,000^e</td> <td>290 fewer per 100,000 (528 fewer to 43 more)</td> </tr> </tbody> </table>	Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Risk with no non-aspirin NSAIDs	Risk difference with non-aspirin NSAIDs (including other non-selective COX inhibitors, preferential COX-2 inhibitors, COX-2 selective inhibitors)	Death from colorectal cancer (CRC mortality) - not reported	-	-	-	-	-	Diagnosis of colorectal cancer (CRC incidence) at 10 years follow-up: mean 8.4 years	53471 (1 non-randomised study) ¹	⊕○○○ Very low ^{a,b,c,d}	HR 0.73 (0.51 to 1.04)	Estimated risk at 10-year timeframe 1,080 per 100,000 ^e	290 fewer per 100,000 (528 fewer to 43 more)	<p>The evidence concerning desirable effects focused on CRC incidence. No studies reporting on CRC mortality were identified.</p> <p>Decision thresholds for desirable effects:</p> <p>CRC mortality:</p> <ul style="list-style-type: none"> ● Trivial/Small: 35 per 100,000 ● Small/Moderate: 95 per 100,000 ● Moderate/Large: 175 per 100,000 <p>CRC incidence:</p> <ul style="list-style-type: none"> ● Trivial/Small: 75 per 100,000 ● Small/Moderate: 200 per 100,000 ● Moderate/Large: 375 per 100,000 <p>The ECICC WG agreed on the judgment 'moderate' regarding desirable effects due to the moderate reduction in CRC cases.</p>
Outcomes	Nº of participants (studies) Follow-up					Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)														
		Risk with no non-aspirin NSAIDs	Risk difference with non-aspirin NSAIDs (including other non-selective COX inhibitors, preferential COX-2 inhibitors, COX-2 selective inhibitors)																			
Death from colorectal cancer (CRC mortality) - not reported	-	-	-	-	-																	
Diagnosis of colorectal cancer (CRC incidence) at 10 years follow-up: mean 8.4 years	53471 (1 non-randomised study) ¹	⊕○○○ Very low ^{a,b,c,d}	HR 0.73 (0.51 to 1.04)	Estimated risk at 10-year timeframe 1,080 per 100,000 ^e	290 fewer per 100,000 (528 fewer to 43 more)																	

1. VITAL study, . Association of Nonsteroidal Anti-Inflammatory Drugs with Colorectal Cancer by Subgroups in the VITamins and Lifestyle (VITAL) Study. *Cancer Epidemiol Biomarkers Prev*; 2015.

a. Risk of bias assessed with ROBINS-I. All the information comes from a study at a moderate risk of bias.

b. We downgraded one level for serious indirectness. Mean age: 67 years (estimated by the reviewer): 19% had age over 70 years. Intervention: any non-aspirin NSAIDs (classical or Coxibs). Intervention dose: 325 mg \geq 1 per week. Use: \geq 4 days per week from 4 to 10 years. We downgraded one level for indirectness because the study considered elderly participants and short intervention use. We judged that this potential indirectness would lower the confidence in estimating our clinical question's effect (defined for a population 50-70 years of age as a base case and a treatment duration of at least ten years).

c. We downgraded for imprecision by two levels. The point estimate of the absolute risk difference exceeds our predefined threshold and points to moderate benefit. However, the CI 95% crosses the null and is compatible from a large benefit to a large harm.

d. We could not assess the risk of publication bias due to the insufficient number of studies per meta-analysis (less than eleven).

e. We estimated the control risk (CR), also known as cumulative risk, in the 50-69 age group, at 10-years' timeframe. First, we obtained the annual incidence rate (IR) of CRC in the 50-69 age group (EU-27): 0.1086% (Source: European Cancer Information System for European Union countries (EU-27), year 2021: <https://ecis.jrc.ec.europa.eu/explorer.php>). Second, we converted the annual IR into the cumulative rate (r) for a 10-year period (IRx10). Third, we converted the r to the CR (%) by using the formula $CR = [1 - \exp(-r)] \times 100$.

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																										
<ul style="list-style-type: none"> ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know 	<p>Date of last search: January 2023</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th data-bbox="275 332 520 776" rowspan="2">Outcomes</th> <th data-bbox="527 332 779 776" rowspan="2">Nº of participants (studies) Follow-up</th> <th data-bbox="785 332 1041 776" rowspan="2">Certainty of the evidence (GRADE)</th> <th data-bbox="1047 332 1142 776" rowspan="2">Relative effect (95% CI)</th> <th colspan="2" data-bbox="1148 332 1495 435">Anticipated absolute effects* (95% CI)</th> </tr> <tr> <th data-bbox="1148 440 1276 776">Risk with no non-aspirin NSAIDs</th> <th data-bbox="1283 440 1495 776">Risk difference with non-aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs, including other non-selective COX inhibitors, preferential COX-2 inhibitors, COX-2 selective inhibitors)</th> </tr> </thead> <tbody> <tr> <td data-bbox="275 781 520 1149" rowspan="2">Cardiovascular event in classical NSAIDs assessed with: unstable angina, arrhythmia, ischemic heart disease, cardiac event, atrial fibrillation, myocardial infarction, heart failure, cardiac arrest, acute coronary syndrome (follow-up: not reported)</td> <td data-bbox="527 781 779 1149" rowspan="2">0 (31 non-randomised studies)^{a,b,c,d}</td> <td data-bbox="785 781 1041 1149" rowspan="2">⊕⊕○○ Low^{e,f,g,h,i}</td> <td data-bbox="1047 781 1142 1149" rowspan="2">RR 1.21 (1.13 to 1.30)</td> <td data-bbox="1148 781 1276 971">5,000 per 100,000^j</td> <td data-bbox="1283 781 1495 971">1,050 more per 100,000 (650 more to 1,500 more)^a</td> </tr> <tr> <td data-bbox="1148 976 1276 1149">20,000 per 100,000^j</td> <td data-bbox="1283 976 1495 1149">4,200 more per 100,000 (2,600 more to 6,000 more)^a</td> </tr> <tr> <td data-bbox="275 1154 520 1481" rowspan="3">Cardiovascular event in Selective Cyclooxygenase-2 Inhibitors (coxibs) assessed with: unstable angina, arrhythmia, ischemic heart disease, cardiac event, atrial fibrillation, myocardial</td> <td data-bbox="527 1154 779 1481" rowspan="3">0 (35 non-randomised studies)^{a,b,c,d}</td> <td data-bbox="785 1154 1041 1481" rowspan="3">⊕⊕○○ Low^{e,h,i,k,l}</td> <td data-bbox="1047 1154 1142 1481" rowspan="3">RR 1.25 (1.08 to 1.45)</td> <td colspan="2" data-bbox="1148 1154 1495 1224">Low</td> </tr> <tr> <td data-bbox="1148 1229 1276 1386">5,000 per 100,000</td> <td data-bbox="1283 1229 1495 1386">1,250 more per 100,000 (400 more to 2,250 more)^a</td> </tr> <tr> <td colspan="2" data-bbox="1148 1391 1495 1481">Moderate</td> </tr> </tbody> </table>	Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Risk with no non-aspirin NSAIDs	Risk difference with non-aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs, including other non-selective COX inhibitors, preferential COX-2 inhibitors, COX-2 selective inhibitors)	Cardiovascular event in classical NSAIDs assessed with: unstable angina, arrhythmia, ischemic heart disease, cardiac event, atrial fibrillation, myocardial infarction, heart failure, cardiac arrest, acute coronary syndrome (follow-up: not reported)	0 (31 non-randomised studies) ^{a,b,c,d}	⊕⊕○○ Low ^{e,f,g,h,i}	RR 1.21 (1.13 to 1.30)	5,000 per 100,000 ^j	1,050 more per 100,000 (650 more to 1,500 more) ^a	20,000 per 100,000 ^j	4,200 more per 100,000 (2,600 more to 6,000 more) ^a	Cardiovascular event in Selective Cyclooxygenase-2 Inhibitors (coxibs) assessed with: unstable angina, arrhythmia, ischemic heart disease, cardiac event, atrial fibrillation, myocardial	0 (35 non-randomised studies) ^{a,b,c,d}	⊕⊕○○ Low ^{e,h,i,k,l}	RR 1.25 (1.08 to 1.45)	Low		5,000 per 100,000	1,250 more per 100,000 (400 more to 2,250 more) ^a	Moderate		<p>The critical outcomes showing undesirable effects were: cardiovascular events, gastrointestinal adverse effects, gastrointestinal ulcers and acute kidney injury.</p> <p>Decision thresholds</p> <p>Major CVD events including CVD mortality:</p> <ul style="list-style-type: none"> ● Trivial/Small: 60 per 100,000 ● Small/Moderate: 162 per 100,000 ● Moderate/Large: 298 per 100,000 <p>Major Gastrointestinal bleeding:</p> <ul style="list-style-type: none"> ● Trivial/Small: 175 per 100,000 ● Small/Moderate: 550 per 100,000 ● Moderate/Large: 950 per 100,000 <p>Gastrointestinal perforation:</p> <ul style="list-style-type: none"> ● Trivial/Small: 125 per 100,000 ● Small/Moderate: 450 per 100,000 ● Moderate/Large: 775 per 100,000 <p>Gastrointestinal ulcer:</p> <ul style="list-style-type: none"> ● Trivial/Small: 250 per 100,000 ● Small/Moderate: 900 per 100,000 ● Moderate/Large: 1550 per 100,000 <p>The ECICC WG agreed on the judgment 'large' regarding undesirable effect considering the increased risk in cardiovascular events, gastrointestinal adverse effects, gastrointestinal ulcers and</p>
Outcomes	Nº of participants (studies) Follow-up					Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)																				
		Risk with no non-aspirin NSAIDs	Risk difference with non-aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs, including other non-selective COX inhibitors, preferential COX-2 inhibitors, COX-2 selective inhibitors)																									
Cardiovascular event in classical NSAIDs assessed with: unstable angina, arrhythmia, ischemic heart disease, cardiac event, atrial fibrillation, myocardial infarction, heart failure, cardiac arrest, acute coronary syndrome (follow-up: not reported)	0 (31 non-randomised studies) ^{a,b,c,d}	⊕⊕○○ Low ^{e,f,g,h,i}	RR 1.21 (1.13 to 1.30)	5,000 per 100,000 ^j	1,050 more per 100,000 (650 more to 1,500 more) ^a																							
				20,000 per 100,000 ^j	4,200 more per 100,000 (2,600 more to 6,000 more) ^a																							
Cardiovascular event in Selective Cyclooxygenase-2 Inhibitors (coxibs) assessed with: unstable angina, arrhythmia, ischemic heart disease, cardiac event, atrial fibrillation, myocardial	0 (35 non-randomised studies) ^{a,b,c,d}	⊕⊕○○ Low ^{e,h,i,k,l}	RR 1.25 (1.08 to 1.45)	Low																								
				5,000 per 100,000	1,250 more per 100,000 (400 more to 2,250 more) ^a																							
				Moderate																								

infarction, heart failure, cardiac arrest, acute coronary syndrome (follow-up: not reported)				20,000 per 100,000 ^m	5,000 more per 100,000 (1,600 more to 9,000 more) ^a	acute kidney injury.
Gastrointestinal adverse effects - Selective Cyclooxygenase-2 Inhibitors (coxibs) - Any follow-up assessed with: any gastrointestinal adverse effects - including ulcer, bleeding and perforation (follow-up: not reported)	0 (28 non-randomised studies) ^{a,d,n,o}	⊕⊕○○ Low ^{e,i,p,q,r}	RR 1.64 (1.44 to 1.86)	Estimated risk at 10-year timeframe		
				1,000 per 100,000 ^s	640 more per 100,000 (440 more to 860 more) ^a	
Gastrointestinal ulcer - Selective Cyclooxygenase-2 Inhibitors (coxibs) follow-up: range 6 weeks to 6 months	0 (4 RCTs) ^{1,2,3,4,a,t}	⊕⊕○○ Low ^{u,v,w,x,y}	RR 2.08 (0.58 to 7.50)	Estimated risk at 10-year timeframe		
				995 per 100,000 ^{s,z}	1,075 more per 100,000 (418 fewer to 6,468 more) ^a	
Major gastrointestinal bleeding - not reported	-	-	-	-	-	
Gastrointestinal perforation - not reported	-	-	-	-	-	
Acute kidney injury - Any follow-up	1482758 (10 non-randomised studies) ^{10,11,12,13,14,5,6,7,8,9,aa}	⊕⊕⊕○ Moderate ^{10,12,15,5,y,ab,ac,ad,ae,af}	OR 1.73 (1.44 to 2.07)	Risk in general population		
				1,600 per 100,000 ^{16,ag}	1,136 more per 100,000 (688 more to 1,656 more)	
<p>1. Schnitzer , . Comparison of the COX-inhibiting nitric oxide donator AZD3582 and rofecoxib in treating the signs and symptoms of Osteoarthritis of the knee..Arthritis Rheumatol; 2005.</p>						

2. Ehrich, . Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group..J Rheumatol; 1999.
3. Laine , . A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib Osteoarthritis Endoscopy Study Group.Gastroenterology; 1999.
4. Bensen, . Treatment of osteoarthritis with celecoxib, a cyclooxygenase- 2 inhibitor: a randomized controlled trial.Mayo Clin Proc; 1999.
5. Schneider , . Association of selective and conventional nonsteroidal antiinflammatory drugs with acute renal failure: a population-based, nested case-control analysis.Am J Epidemiol; 2006.
6. Perez Gutthann , . Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure.Arch Intern Med; 1996.
7. Murray, . Ibuprofen associated renal impairment in a large general internal medicine practice.Am J Med Sci; 1990.
8. Leonard , . Proton pump inhibitors and traditional nonsteroidal anti-inflammatory drugs and the risk of acute interstitial nephritis and acute kidney injury.Pharmacoepidemiol Drug Safety; 2012.
9. Lafrance, . Selective and non-selective non-steroidal antiinflammatory drugs and the risk of acute kidney injury.Pharmacoepidemiol Drug Safety; 2009.
10. Huerta, . Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population.Am J Kidney Dis; 2005.
11. Henry, . Consumption of non-steroidal anti-inflammatory drugs and the development of functional renal impairment in elderly subjects. Results of a case-control study.Br J Clin Pharmacol; 1997.
12. Griffin, . Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons.Am J Epidemiol; 2000.
13. Evans, . Non-steroidal anti-inflammatory drugs and hospitalization for acute renal failure.QJM; 1995.
14. Bouvy , . Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors.Drug Saf; 2003.
15. Nelson, . Association of nonsteroidal anti-inflammatory drug prescriptions with kidney disease among active young and middle-aged adults.JAMA Netw Open; 2019.
16. Susantitaphong, . Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: a meta-analysis.Clin J Am Soc Nephrol; 2013.

a. Number of participants was not reported.

b. The references of the meta-analysed studies are not provided in the systematic review report.

c. Based on the systematic review: Martín-Arias LH et al. Cardiovascular Risk of Nonsteroidal Anti-inflammatory Drugs and Classical and Selective Cyclooxygenase-2 Inhibitors: A Meta-analysis of Observational Studies. J Clin Pharmacol. 2019 Jan;59(1):55-73.

d. Cohort or case-control studies.

e. The meta-analysis included studies with a Newcastle Ottawa Scale (NOS) score of at least 5. Moreover, a sensitivity analysis excluding studies with NOS scores of 5 or 6 did differ significantly from the initial result.

f. We considered a consistent direction of effect across studies as indication of clinically irrelevant heterogeneity despite a high I² (75%). Thus, we did not downgrade for inconsistency.

g. We did not downgrade for indirectness. Adults were on active classical NSAIDs (non-aspirin) treatment for any health problem. The population was heterogeneous in terms of age (from young adults to old people), colorectal cancer risk, and CV risk. The interventions assessed were diclofenac, ibuprofen and naproxen. Intervention doses (low and high doses were included) and the treatment duration (from 4 months to 20 years) were heterogeneous. The outcomes follow-ups were not reported. We judged that this potential indirectness would not lower the confidence in estimating our clinical question's effect (defined for a population 50-70 years of age as a base case and a treatment duration of at least ten years).

h. We did not downgrade for imprecision. The point estimate of the absolute risk difference exceeds our predefined threshold and points to a large harm. The CI 95% does not cross the null and is always compatible with large harm.

i. Publication bias was not detected (Egger test performed but p value not reported).

j. Baseline risk estimates for low-risk and moderate-risk of developing CVD events including CVD mortality at 20 years were extrapolated based on the FRAMINGHAM score.

k. We considered a consistent direction of effect across studies as indication of clinically irrelevant heterogeneity despite a high I² (81%). Thus, we did not downgrade for inconsistency.

l. We did not downgrade for indirectness. Adults were on coxibs treatment for any health problem. The population was heterogeneous in terms of age (from young adults to old people), colorectal cancer risk, and CV risk. The interventions assessed were Celecoxib, Etoricoxib, Rofecoxib and Valdecoxib. Intervention doses (low and high doses were included) and the treatment duration (from 4 months to 20 years) were heterogeneous. The outcomes follow-ups were not reported. We judged that this potential indirectness would not lower the confidence in estimating our clinical question's effect (defined for a population 50-70 years of age as a base case and a treatment duration of at least ten years).

m. Median of the control risks in the meta-analysed studies in the AAS SoF.

n. Based on the systematic review Martín Arias LH, et al. Gastrointestinal safety of coxibs: systematic review and meta-analysis of observational studies on selective inhibitors of cyclo-oxygenase 2. *Fundam Clin Pharmacol.* 2019 Apr;33(2):134-147.

o. The references of the meta-analysed studies will be provided by the systematic review team.

p. We considered a consistent direction of effect across studies as indication of clinically irrelevant heterogeneity despite a high I2 (73%). Thus, we did not downgrade for inconsistency.

q. We did not downgrade for indirectness. Adults were on coxibs treatment for any health problem. The population was heterogeneous in terms of age (from young adults to old people), colorectal cancer risk, and CV risk. The interventions were Celecoxib, Etoricoxib, Rofecoxib and Valdecoxib. Intervention doses (low and high doses were included) and the treatment duration (from 1 year to 15 years) were heterogeneous. The outcomes follow-ups were not reported. We judged that this potential indirectness would not lower the confidence in estimating our clinical question's effect (defined for a population 50-70 years of age as a base case and a treatment duration of at least ten years).

r. We did not downgrade for imprecision. The point estimate of the absolute risk difference exceeds our predefined threshold and points to moderate harm. The CI 95% does not cross the null and is always compatible from small to large harm.

s. We estimated the control risk (CR), also known as cumulative risk, for a 10-year period of intervention use. First, we obtained the annual incidence rate (IR) of gastrointestinal ulcers from a systematic review: 0.10% (doi: 10.1016/S0895-4356(01)00461-9). Second, we converted the annual IR into the cumulative rate (r) for a 10-year period (IRx10). Third, we converted the r to the CR (%) by using the formula: $CR = [1 - \exp(-r)] \times 100$.

t. Based on the systematic review: Curtis E, et al. Safety of Cyclooxygenase-2 Inhibitors in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. *Drugs Aging*. 2019 Apr;36(Suppl 1):25-44.

u. No study was assessed at a high risk of bias.

v. I2: 0%.

w. We did not downgrade for indirectness. Adults were on coxibs treatment for osteoarthritis pain management (mainly knee pain). The patients' mean age ranged from 60 to 64 years. The interventions were Celecoxib (100 mg daily) and Rofecoxib (25 mg daily). The treatment duration was short, ranging from 1.5 to 6 months. The follow-up was done during the trial. We judged that this potential indirectness would not lower the confidence in estimating our clinical question's effect (defined for a population 50-70 years of age as a base case and a treatment duration of at least ten years).

x. We downgraded for imprecision by two levels. The point estimate of the absolute risk difference exceeds our predefined threshold and points to moderate harm. However, the CI 95% crosses the null and is compatible from a small benefit to a large harm.

y. We could not assess the risk of publication bias due to the insufficient number of studies per meta-analysis (less than eleven).

z. Decision thresholds defined by the ECICC for the absolute effect on gastrointestinal ulcer (judged half as bad as a gastrointestinal perforation): Trivial/Small: 250 per 100,000; b) Small/Moderate: 900 per 100,000; c) Moderate/Large: 1,550 per 100,000.

aa. Based on the systematic review Zhang X, et al. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. BMC Nephrol. 2017 Aug 1;18(1):256.

ab. Study quality was evaluated with the Newcastle-Ottawa Assessment Scale (NOS). No study was assessed as low quality. Hence, the quality was considered as medium to high.

ac. We considered a consistent direction of effect across studies as an indication of clinically irrelevant heterogeneity despite a high I² (89%). Thus, we did not downgrade for inconsistency.

ad. We did not downgrade for indirectness. Participants were using NSAIDs for any reason. Five of the ten included studies considered participants older than 65 years old. Traditional NSAIDs and COX-2 inhibitors were included except for low-dose aspirin (<300 mg per dose). Most of the studies used NSAIDs between one and three months before index. Studies used various definitions of acute kidney injury, with AKI defined by ICD 9 or 10 codes, or change in estimated glomerular filtration rate, creatinine clearance or serum creatinine. We judged that this potential indirectness would not lower the confidence in estimating our clinical question's effect (defined for a population 50-70 years of age as a base case and a treatment duration of at least ten years).

ae. We did not downgrade for imprecision. The point estimate of the absolute risk difference exceeds our predefined threshold and points to large harm. The CI 95% does not cross the null and is always compatible with moderate to large harm.

af. We found evidence suggesting dose-response relationship between non-Aspirin NSAIDs use and acute kidney injury. Nelson 2019, a retrospective, longitudinal cohort study of active young and middle-aged adults (n=764,228), found a dose-response for acute kidney injury (patients with 1-7 defined daily doses(DDDs)/month in the previous 6 months: adjusted HR: 1.1, CI 95%: 1.0 to 1.2; patients with > 7 DDDs/month: adjusted HR: 1.2, CI 95%: 1.1 to 1.4). A dose-response relationship was also suggested in Griffin 20002, Huerta 20052 and Schneider 20062 (observational studies included in the Zhang 2017 review).

ag. Incidence rate of acute kidney injury in the community (any age): 8.3% (CI 95%: 1.6 to 33). We took 1.6%, the lowest extreme of the CI, as it is more plausible for people at average risk of CRC.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Very low ○ Low ○ Moderate ○ High ○ No included studies 		<p>Based on the assessment of the desirable and undesirable effects discussed, the ECICC Working Group agreed on the judgment 'very low' regarding the certainty of evidence as this was the lowest certainty among the critical outcomes.</p>

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability 		<p>Trade-offs of disutility between nonfatal stroke (thrombotic or hemorrhagic) and GI bleedings were in the range of 2:1 to 3:1 and between myocardial infarction and bleeds of 1:1 to 2:1. (33)</p> <p>For consistency with the judgment on the healthcare question addressing low-dose aspirin, the WG agreed on the judgment of 'probably no important uncertainty or variability'.</p>

Outcome	Research evidence	Interpretation of findings
---------	-------------------	----------------------------

Diagnosis of Colorectal Cancer (colorectal cancer incidence)	<p>1 SR with 6 cross-sectional studies with patients with colorectal cancer⁽¹⁷⁻²⁰⁾ (1,456 participants)</p> <p>Utilities (Indirect measures [HUI and EQ5D])</p> <p>Healthy = 1.0</p> <p>Stage I = 0.84 (0.17) to 0.83 (0.14)</p> <p>Stage II = 0.86 (0.14) to 0.86 (0.12)</p> <p>Stage III = 0.85 (0.14) to 0.82 (0.13)</p> <p>Stage IV = 0.84 (0.12) to 0.66 (0.30)</p> <p>Utilities (Direct measures [VAS])</p> <p>Stage IV = 0.75 to 0.59</p> <p>*All data reported as mean (SD)</p>	<p>Studies conducted in patients with a colorectal cancer diagnosis show that people exhibit lower utilities after a colorectal cancer diagnosis as compared to healthy populations, and a slight decrease in utilities when the disease progresses to stage IV.</p>
---	--	--

Death from colorectal cancer (colorectal cancer mortality)	<p>1 SR with 13 quantitative⁽¹⁷⁻¹⁹⁾ and three qualitative studies⁽²⁰⁻²²⁾ with average-risk adults undergoing colorectal cancer screening (8,692 participants)</p> <p>Results suggest that people place a high value in reducing the risk of death after a colorectal cancer screening. A reduction in risk of death, as well as a reduction in colorectal cancer incidence, are perceived by the participants as one of the most important attributes of tests</p>	<p>Indirect evidence from studies involving average-risk adults undergoing colorectal cancer screening indicates that individuals place a high value in reducing the risk of death while participating in screening. Participants perceive a decrease in the risk of death, along with a reduction in colorectal cancer incidence, as the most significant attributes.</p>
---	--	--

Harms (major GI bleeding, GI perforation, GI ulcer)	<p>Major GI bleeding</p> <p>Major GI bleeding (from major bleeding)</p> <p>1 SR⁽²³⁾ including 2 primary studies with patients with acute myocardial infarction receiving antiplatelet drugs (12,850 participants)</p> <p>Utility (Indirect measures [EQ5D])</p> <p>Decrements from baseline to 6 months after dual antiplatelet therapy -0.045 (-0.07 to -0.02)</p> <p>*All data reported as mean (95% CI)</p> <p>Major GI bleeding (from GI bleeding)</p> <p>1 SR⁽²⁴⁾ including 3 primary studies with adults with thromboembolic events undergoing anticoagulation therapy (1,217 participants)</p> <p>The mean utilities ranged from 0.59 (EQ-5D) to 0.65 (SG and TTO).</p> <p>GI perforation</p> <p>1 SR with 2 qualitative studies^(25, 26) with average-risk adults considering colorectal cancer screening (56 participants)</p> <p>Results suggest that the risk of bowel perforation may be a significant concern for patients considering colorectal cancer screening.</p> <p>GI ulcer</p> <p>No studies were found.</p>	<p>Indirect evidence suggests that people find a major gastrointestinal bleeding event to have a moderate impact on their lives.</p> <p>Indirect evidence from studies on average-risk adults undergoing a colorectal cancer screening suggest that people have a significant concern with GI perforation when considering to undergo health care interventions.</p>
--	---	--

All severe stroke/including Haemorrhagic Stroke	<p>1 SR⁽²⁷⁾ including 7 primary studies with adult patients that experienced ischemic or hemorrhagic stroke at least 3 months prior (sample size was not reported)</p> <p>Utilities (Indirect measures [EQ5D])</p> <p>Ischemic stroke: 0.68 (0.60 to 0.76)</p> <p>Hemorrhagic stroke: 0.58 (0.39 to 0.77)</p> <p>*All data reported as mean (95% CI)</p>	<p>Stroke patients exhibit a lower health utility in hemorrhagic stroke than in ischemic stroke. However, there is wide variability for hemorrhagic stroke.</p>
--	---	---

Cardiovascular Events	<p>Includes Heart Failure, Arrhythmia, Myocardial Infarction, Transient Ischaemic Attack</p> <p>Chronic heart failure</p> <p>1 SR⁽²⁸⁾ including 35 studies with a variety of patient types, including general population (31,308 participants)</p> <p>Utilities (Indirect measures [EQ5D])</p> <p>Chronic heart failure: 0.64-0.72</p> <p>NYHA class I: 0.79-0.86</p> <p>NYHA class II: 0.75-0.81</p> <p>NYHA class III: 0.61-0.69</p> <p>NYHA class IV: 0.51-0.66</p> <p>* All data reported as Q1 and Q3 limits.</p> <p>Arrhythmia</p> <p>1 SR⁽²⁹⁾ including 1 primary study with participants with cardiovascular diseases (16,712 participants)</p> <p>Utilities (Indirect measures [EQ5D])</p> <p>Arrhythmia: 0.70 (0.16).</p> <p>*All data reported as mean (SD)</p> <p>Myocardial Infarction</p> <p>1 SR⁽³⁰⁾ including 70 studies with participants that had myocardial infarction over time (pre-post 2013) (sample size not provided)</p> <p>Utilities (Indirect measures [EQ5D])</p> <p>Myocardial Infarction: 0.72 (0.68-0.76) pre-2013 (n = 38 studies) to 0.79 (0.73-0.85) post-2013 (n = 32 studies)</p> <p>*All data reported as median (IQR)</p> <p>Transient ischaemic attack</p> <p>1 SR⁽³¹⁾ including 1 primary study with adults from general practices</p>	<p>Studies conducted in patients with chronic heart failure show that people find that the disease has a low to moderate impact on their lives, exhibiting progressively lower utility (or higher disutility) as functional capacity decreases.</p> <p>People find arrhythmia to have a moderate impact on their lives.</p> <p>Studies conducted in patients that experienced myocardial infarction show that people exhibit higher utilities over time (pre-post 2013), likely due to types of studies being conducted (increase in trials eliciting utilities), the patient populations being evaluated (in particular, changes in disease severity and duration of disease).</p> <p>People find a transient ischaemic attack event to have a moderate impact on their lives.</p>
------------------------------	---	---

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know 		<p>The WG previously judged that the identified evidence suggested moderate benefits, large harms, very low certainty of the evidence and probably no important uncertainty or variability.</p> <p>Thus, the WG considered the balance between desirable and undesirable effects “favours the comparison”</p>

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS										
<ul style="list-style-type: none"> ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	<p>Drug unit costs extracted from the studies included in the cost-effectiveness review</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Study</th> <th>Drug</th> <th>Cost (US\$, year)</th> <th>Cost (€, 2022)*</th> <th>Source</th> </tr> </thead> <tbody> <tr> <td>Ladabaum, 2003 (US)</td> <td>COX-2 inhibitor cost per day</td> <td>US\$ 1.00 (1998)</td> <td>€ 1.15</td> <td>Estimated by authors, based on retail cost to the pharmacy at the University of California, San Francisco.</td> </tr> </tbody> </table> <p>* Cost Euro 2022: Harmonised Index of Consumer Prices (HICP, Eurostat) and Purchasing Power Parity (PPP Euro, Eurostat) for 2022 were used for adjustment.</p>	Study	Drug	Cost (US\$, year)	Cost (€, 2022)*	Source	Ladabaum, 2003 (US)	COX-2 inhibitor cost per day	US\$ 1.00 (1998)	€ 1.15	Estimated by authors, based on retail cost to the pharmacy at the University of California, San Francisco.	<p>The study of Ladabaum et al 2003 (US) includes a unit cost of celecoxib calculated for the year 1998. Despite the two decades, since this publication, prices remain similar. For example, the retail price of celecoxib (generic) in Spain is 22.49 euros for the 100 mg / 30-capsule presentation (2023) (0,75 euros per day).</p> <p>The WG agreed on the judgment ‘moderate costs’.</p>
Study	Drug	Cost (US\$, year)	Cost (€, 2022)*	Source								
Ladabaum, 2003 (US)	COX-2 inhibitor cost per day	US\$ 1.00 (1998)	€ 1.15	Estimated by authors, based on retail cost to the pharmacy at the University of California, San Francisco.								

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ○ Low ○ Moderate ○ High ● No included studies 	Drug unit costs extracted from the studies included in the cost-effectiveness review. The evaluation of the certainty of the evidence does not apply.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE						ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ● Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies 	Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	ICER	Incremental cost per patient (Euro, 2022)*	Incremental effect per patient (LYG)	<p>Only one observational study provided information on the cost-effectiveness related to the COX-2-specific inhibitors, and this favoured the comparison.</p> <p>The WG agreed on the judgment ‘favors the comparison’.</p>
	Non-aspirin NSAIDs / no intervention (LYG)	1 observational study) ¹	⊕⊕⊕○ Moderate ^a	270,729.08 €/LYG	7,038.96 €	0.026	
<p>1. Ladabaum, U, Scheiman, JM, Fendrick, AM. Potential effect of cyclooxygenase-2-specific inhibitors on the prevention of colorectal cancer: a cost-effectiveness analysis. Am J Med; 2003.</p> <p>a. Some parts of the model description are unclear. The model is not validated.</p> <p>* Cost per person Euro 2022: Harmonised Index of Consumer Prices (HICP, Eurostat) and Purchasing Power Parity (PPP Euro, Eurostat) for 2022 were used for adjustment</p>							

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know 	No studies were identified.	<p>The WG discussed how, compared to Aspirin, the out-of-pocket cost of non-aspirin NSAIDs would be higher.</p> <p>Thus, the WG agreed on the judgment of 'probably reduced'.</p>

Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS										
<ul style="list-style-type: none"> ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know 	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 15%;">Outcome</th> <th style="width: 45%;">Studies / No. of participants / Estimates</th> <th style="width: 40%;">Interpretation of findings</th> </tr> </thead> <tbody> <tr> <td>Adherence</td> <td>- 1 SR⁽¹⁾ including 29 studies with mixed populations, mostly with average-risk participants (52,189 participants). In aspirin trials, day-to-day adherence estimates varied (30.0–100.0%), however 82% (18/22 studies) reported high adherence rates of aspirin (≥80.0% adherence levels). At eight years, 64.0% of participants in one trial were classed as adherent. By 15 years, 46.0% were adherent. No studies examined adherence in routine care.</td> <td rowspan="3">Very indirect evidence suggests that the likelihood that eligible users of NSAIDs would accept it and use it may be moderate to high, depending on their perceived need for taking it and perceived risks that are associated with it. In the long-term, there is likely important uncertainty on whether people would keep using NSAIDs.</td> </tr> <tr> <td>Persistence of use Defined as the length of time between uptake and last dose</td> <td>- 1 SR⁽¹⁾ including 15 studies with mixed populations, mostly with average-risk participants (46,629 participants). Short-term persistence (i.e. weeks, months) was high (83.3–100%). The proportion of participants reporting long-term persistence (i.e. years) varied. One randomized controlled trial observed high levels of persistence, with 93.6% of participants still taking aspirin (at least 50% of the medication), at year three. In contrast, two trials reported low to moderate levels of persistence, with 38.6% and 66.8% of participants completing the three-year medication.</td> </tr> <tr> <td>Willingness to take</td> <td>- 1 SR⁽¹⁾ including four studies with mixed populations, mostly average-risk participants (687 participants). Results suggest a moderate to high willingness from participants to use aspirin for cancer prevention (43.6–76.0%). - 1 SR⁽²⁾ including 20 qualitative studies with people at average-risk of colorectal cancer. People are more likely to use NSAIDs if there is a strong-perceived need, this being mainly determined by health status and age, and are most likely to be influenced by both health professionals and their family. Perceptions of risk and benefit also influence decision-making and use.</td> </tr> </tbody> </table> <p>NSAIDs: Non-steroidal anti-inflammatory drugs</p> <p>References1. Lloyd KE, Hall LH, King N, Thornehoe RJ, Rodriguez-Lopez R, Ziegler L, Taylor DG, MacKenzie M, Smith SG; AsCaP Group. Aspirin use for cancer prevention: A systematic review of public, patient and healthcare provider attitudes and adherence behaviours. <i>Prev Med.</i> 2022 Jan;154:106872. doi: 10.1016/j.ypmed.2021.106872.</p> <p>2. Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, Maguire C, Hind D, Tappenden P. Chemoprevention of colorectal cancer: systematic review and economic evaluation. <i>Health Technol Assess.</i> 2010 Jun;14(32):1-206. doi: 10.3310/hta14320.</p>	Outcome	Studies / No. of participants / Estimates	Interpretation of findings	Adherence	- 1 SR ⁽¹⁾ including 29 studies with mixed populations, mostly with average-risk participants (52,189 participants). In aspirin trials, day-to-day adherence estimates varied (30.0–100.0%), however 82% (18/22 studies) reported high adherence rates of aspirin (≥80.0% adherence levels). At eight years, 64.0% of participants in one trial were classed as adherent. By 15 years, 46.0% were adherent. No studies examined adherence in routine care.	Very indirect evidence suggests that the likelihood that eligible users of NSAIDs would accept it and use it may be moderate to high, depending on their perceived need for taking it and perceived risks that are associated with it. In the long-term, there is likely important uncertainty on whether people would keep using NSAIDs.	Persistence of use Defined as the length of time between uptake and last dose	- 1 SR ⁽¹⁾ including 15 studies with mixed populations, mostly with average-risk participants (46,629 participants). Short-term persistence (i.e. weeks, months) was high (83.3–100%). The proportion of participants reporting long-term persistence (i.e. years) varied. One randomized controlled trial observed high levels of persistence, with 93.6% of participants still taking aspirin (at least 50% of the medication), at year three. In contrast, two trials reported low to moderate levels of persistence, with 38.6% and 66.8% of participants completing the three-year medication.	Willingness to take	- 1 SR ⁽¹⁾ including four studies with mixed populations, mostly average-risk participants (687 participants). Results suggest a moderate to high willingness from participants to use aspirin for cancer prevention (43.6–76.0%). - 1 SR ⁽²⁾ including 20 qualitative studies with people at average-risk of colorectal cancer. People are more likely to use NSAIDs if there is a strong-perceived need, this being mainly determined by health status and age, and are most likely to be influenced by both health professionals and their family. Perceptions of risk and benefit also influence decision-making and use.	<p>The WG discussed the administration of non-aspirin NSAIDs and concluded that the intervention itself is acceptable.</p> <p>However, while initial adherence to the medication is high, it may decrease over time due to the long-term use of the treatment.</p> <p>Health care professionals:</p> <p>Healthcare professionals may be hesitant to prescribe non-aspirin NSAIDs for extended periods if they are unable to also prescribe proton-pump inhibitors (PPIs) to mitigate the risk of gastric ulcers.</p>
Outcome	Studies / No. of participants / Estimates	Interpretation of findings										
Adherence	- 1 SR ⁽¹⁾ including 29 studies with mixed populations, mostly with average-risk participants (52,189 participants). In aspirin trials, day-to-day adherence estimates varied (30.0–100.0%), however 82% (18/22 studies) reported high adherence rates of aspirin (≥80.0% adherence levels). At eight years, 64.0% of participants in one trial were classed as adherent. By 15 years, 46.0% were adherent. No studies examined adherence in routine care.	Very indirect evidence suggests that the likelihood that eligible users of NSAIDs would accept it and use it may be moderate to high, depending on their perceived need for taking it and perceived risks that are associated with it. In the long-term, there is likely important uncertainty on whether people would keep using NSAIDs.										
Persistence of use Defined as the length of time between uptake and last dose	- 1 SR ⁽¹⁾ including 15 studies with mixed populations, mostly with average-risk participants (46,629 participants). Short-term persistence (i.e. weeks, months) was high (83.3–100%). The proportion of participants reporting long-term persistence (i.e. years) varied. One randomized controlled trial observed high levels of persistence, with 93.6% of participants still taking aspirin (at least 50% of the medication), at year three. In contrast, two trials reported low to moderate levels of persistence, with 38.6% and 66.8% of participants completing the three-year medication.											
Willingness to take	- 1 SR ⁽¹⁾ including four studies with mixed populations, mostly average-risk participants (687 participants). Results suggest a moderate to high willingness from participants to use aspirin for cancer prevention (43.6–76.0%). - 1 SR ⁽²⁾ including 20 qualitative studies with people at average-risk of colorectal cancer. People are more likely to use NSAIDs if there is a strong-perceived need, this being mainly determined by health status and age, and are most likely to be influenced by both health professionals and their family. Perceptions of risk and benefit also influence decision-making and use.											

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know 	<p>Indirect evidence from only a few countries that have issued guidance recommending aspirin for cancer prevention is available. These guidelines recommend aspirin for specific populations (e.g. people with Lynch syndrome, people with a 10-year cardiovascular disease risk of at least 10%, and not at high risk for bleeding or people aged 50–70 years who are at average risk of colorectal cancer) (1).</p> <p>One systematic review found high levels of adherence on a day-to-day basis in trials with mixed populations, mostly with average-risk participants. At short-term follow-up, most people were still taking aspirin, but evidence was mixed at long-term (38.6 to 93.6% of participants completing the third year of treatment). The systematic review found no studies examining uptake and adherence in routine care, and, therefore, a substantial scope for research into the barriers and facilitators to implementing aspirin for colorectal cancer preventive therapy into clinical care (2).</p> <p>Most guidelines do not recommend routine aspirin use for primary prevention of cardiovascular disease in general populations (3-5), and that implementation of those recommendations in specific populations could result in inappropriate use or prescription in a substantial proportion of participants (e.g. approximately 28% of participants aged <40 or >70 years taking aspirin without a recommended indication) (6, 7).</p> <p>References</p> <ol style="list-style-type: none"> 1. Liang PS, Shaikat A, Crockett SD. AGA Clinical Practice Update on Chemoprevention for Colorectal Neoplasia: Expert Review. <i>Clin Gastroenterol Hepatol.</i> 2021;19(7):1327-1336. doi:10.1016/j.cgh.2021.02.014 2. Lloyd KE, Hall LH, King N, Thorneloe RJ, Rodriguez-Lopez R, Ziegler L, Taylor DG, MacKenzie M, Smith SG; AsCaP Group. Aspirin use for cancer prevention: A systematic review of public, patient and healthcare provider attitudes and adherence behaviours. <i>Prev Med.</i> 2022 Jan;154:106872. doi: 10.1016/j.ypmed.2021.106872. 3. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. <i>J Am Coll Cardiol.</i> 2019;74(10):e177-e232. doi:10.1016/j.jacc. 2019.03.010 4. Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease. SIGN publication 149. 5. National Institute for Health and Care Excellence Clinical Knowledge Summaries. Antiplatelet treatment: primary prevention of CVD. Revised 2021. https://www.aspirin-foundation.com/scientific-information/guidelines/uk-guidelines-aspirin. 6. Hira RS, Gosch KL, Kazi DS, Yeh RW, Kataruka A, Maddox TM, Shah T, Jneid H, Bhatt DL, Virani SS. Potential Impact of the 2019 ACC/AHA Guidelines on the Primary Prevention of Cardiovascular Disease Recommendations on the Inappropriate Routine Use of Aspirin and Aspirin Use Without a Recommended Indication for Primary Prevention of Cardiovascular Disease 	<p>The WG considered the non-aspirin NSAIDs probably feasible to implement.</p>

in Cardiology Practices: Insights From the NCDR PINNACLE Registry. Circ Cardiovasc Qual Outcomes. 2022 Mar;15(3):e007979. doi: 10.1161/CIRCOUTCOMES.121.007979.7. Almagal N, Cainzos-Achirica M, McEvoy JW. Mind the Gap: Primary Prevention Aspirin and the Danger of Suboptimal Implementation of Contemporary Guidelines Into Clinical Practice. Circ Cardiovasc Qual Outcomes. 2022 Mar;15(3):e008799. doi: 10.1161/CIRCOUTCOMES.121.008799.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

JUDGEMENT							
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ●	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
---	--	---	--	---

CONCLUSIONS

Recommendation

The ECICC Working Group (WG) recommends not using non-aspirin NSAIDs for primary prevention of colorectal cancer in asymptomatic adults with average risk of colorectal cancer (strong recommendation, very low certainty of the evidence).

Justification

The recommendation against the use of non-aspirin NSAIDs for primary prevention of colorectal cancer in adults at average risk is based on an evaluation of benefits and harms.

The Working Group strongly recommended not following the intervention due to low or very low certainty of evidence for benefits while there are potential large harms with moderate certainty evidence for acute kidney injury and very low certainty for cardiovascular disease, severe stroke, and gastrointestinal ulcers.

Despite stronger evidence being available only for acute kidney injury, the Working Group determined that the risk is significant, serious, and well-supported by dose-response evidence, justifying a strong recommendation not to use long-term non-aspirin NSAIDs. Additionally, the working group agreed that any inconsistencies in the evidence are not serious since they can be explained by variations in dosage and duration of non-aspirin NSAIDs use.

Differences in acute kidney injury outcomes result depend on the dose and how long a patient has taken non-aspirin NSAIDs, leading to varying relative effects and apparent inconsistencies in reported outcomes.

The Working Group also agreed that there is no serious indirectness in the evidence as harms associated with cardiovascular disease, severe stroke, acute kidney injury, and gastrointestinal ulcers are applicable to the population of interest. Furthermore, more cost-effective options that provide more benefits are available to patients. Therefore, the working group decided non-aspirin NSAIDs should not be long-term prescribed in adults at average risk for primary prevention of colorectal cancer.

At the decision-making phase, a vote among the Working Group took place with the following outcome:

- 7 members voted for a strong recommendation against the intervention

- 1 member voted for a conditional recommendation against the intervention
- 2 members abstained

Subgroup considerations

None were considered by the working group.

Implementation considerations

None were considered by the working group.

Monitoring and evaluation

Quality indicators for monitoring the implementation of this recommendation are planned for development.

Research priorities

Further studies are needed to have more data on the efficacy and safety of non-aspirin NSAIDs for primary prevention of colorectal cancer in adults at average risk.

Updated meta-analysis considering updated evidence of cardiovascular disease and the use of non-aspirin NSAIDs.