



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 low-dose aspirin vs. no low-dose aspirin be used for primary prevention of colorectal cancer in average risk adults?	
POPULATION:	Asymptomatic adults, aged 50-70, at average risk of colorectal cancer
INTERVENTION:	Low-dose aspirin
COMPARISON:	No low-dose aspirin
MAIN OUTCOMES:	Death from colorectal cancer; Diagnosis of colorectal cancer; Major Cardiovascular (CVD) events; Major gastrointestinal bleeding; Gastrointestinal ulcer; Chronic kidney disease; Intracranial hemorrhage
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) (1).</p> <p>The ECICC Working Group (WG) has prioritized this question considering existing disparities in recommendations from guideline organizations and limitations of current systematic reviews, which focus narrowly on effectiveness while overlooking critical factors such as patient values, resource implications, equity, acceptability, and feasibility.</p>
CONFLICT OF INTERESTS:	Conflicts of interest (CoI) for ECICC 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. For more information visit: <a href="https://healthcare-quality.jrc.ec.europa.eu/en/ecicc/discover-ecicc/working-groups">https://healthcare-quality.jrc.ec.europa.eu/en/ecicc/discover-ecicc/working-groups</a> .

## ASSESSMENT

Problem		
Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<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>This healthcare question focused on whether low-dose aspirin should be used for primary prevention of CRC in asymptomatic average risk adults.</p>

Beyond these measures, chemoprevention, particularly with aspirin, has been extensively investigated as a strategy to reduce CRC incidence and its precursor lesions. The use of aspirin for CRC prevention remains controversial, as its potential benefits must be weighed against the risks of adverse effects.

The WG prioritised this question for the ECICC given conflicting recommendations and recent changes in recommendations of other organizations.

## Desirable Effects

How substantial are the desirable anticipated effects?

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<ul style="list-style-type: none"> <li>○ Trivial</li> <li>○ Small</li> <li>○ Moderate</li> <li>● Large</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Date of last search: October 2025</p> <table border="1"> <thead> <tr> <th>Outcomes</th> <th>Nº of participants (studies) Follow-up</th> <th>Certainty of the evidence (GRADE)</th> <th>Relative effect (95% CI)</th> <th>Anticipated absolute effects* (95% CI)</th> </tr> <tr> <td></td> <td></td> <td></td> <td></td> <td> <table border="1"> <thead> <tr> <th>Risk with No low-dose aspirin</th> <th>Risk difference with Low-dose aspirin</th> </tr> </thead> <tbody> <tr> <td>Estimated risk at 20-year timeframe</td> <td></td> </tr> <tr> <td>668 per 100,000<sup>i</sup></td> <td><b>173 fewer per 100,000</b> (259 fewer to 66 fewer)</td> </tr> <tr> <td>High</td> <td></td> </tr> <tr> <td>0 per 100,000</td> <td><b>0 fewer per 100,000</b> (0 fewer to 0 fewer)</td> </tr> </tbody> </table> </td> </tr> <tr> <td>Death from colorectal cancer (CRC mortality) at 10- 20 years follow-up: range 10 years since the intervention start to 18 years</td> <td>53909 (5 RCTs)<sup>1,2,3,4,5,a,b,c</sup></td> <td>⊕⊕○○ Low<sup>d,e,f,g,h</sup></td> <td><b>OR 0.74</b> (0.61 to 0.90)</td> <td></td> </tr> <tr> <td>Diagnosis of colorectal cancer (CRC incidence) after 10 years</td> <td>69535 (4 RCTs)<sup>1,2,5,6,b,j,k</sup></td> <td>⊕⊕⊕⊕</td> <td><b>OR 0.64</b> (0.52 to</td> <td>Estimated risk at 20-year timeframe</td> </tr> </thead></table>	Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)					<table border="1"> <thead> <tr> <th>Risk with No low-dose aspirin</th> <th>Risk difference with Low-dose aspirin</th> </tr> </thead> <tbody> <tr> <td>Estimated risk at 20-year timeframe</td> <td></td> </tr> <tr> <td>668 per 100,000<sup>i</sup></td> <td><b>173 fewer per 100,000</b> (259 fewer to 66 fewer)</td> </tr> <tr> <td>High</td> <td></td> </tr> <tr> <td>0 per 100,000</td> <td><b>0 fewer per 100,000</b> (0 fewer to 0 fewer)</td> </tr> </tbody> </table>	Risk with No low-dose aspirin	Risk difference with Low-dose aspirin	Estimated risk at 20-year timeframe		668 per 100,000 <sup>i</sup>	<b>173 fewer per 100,000</b> (259 fewer to 66 fewer)	High		0 per 100,000	<b>0 fewer per 100,000</b> (0 fewer to 0 fewer)	Death from colorectal cancer (CRC mortality) at 10- 20 years follow-up: range 10 years since the intervention start to 18 years	53909 (5 RCTs) <sup>1,2,3,4,5,a,b,c</sup>	⊕⊕○○ Low <sup>d,e,f,g,h</sup>	<b>OR 0.74</b> (0.61 to 0.90)		Diagnosis of colorectal cancer (CRC incidence) after 10 years	69535 (4 RCTs) <sup>1,2,5,6,b,j,k</sup>	⊕⊕⊕⊕	<b>OR 0.64</b> (0.52 to	Estimated risk at 20-year timeframe
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 The ECICC working group discussed that aspirin for primary prevention would require long-term use and agreed to focus on data from extended follow-up periods and longer treatment durations.  As such, and to ensure consistency in evidence assessment, a base-case scenario was defined:   - Population: Adults at average risk, aged 50–70 years - Treatment duration: At least 10 years   **Duration of Aspirin use:**  Subgroup analyses done for subsets of participants in the NHS and the Swedish studies showed differences in CRC incidence according to Aspirin use duration (test for subgroup differences: Chi<sup>2</sup> = 8.49, df = 2; P = 0.01).  This suggests that more prolonged Aspirin use is associated with a reduction in CRC incidence:   - Short treatment duration (5 to 10 years): HR 0.92, 95% CI 0.80 to 1.06 - Intermediate treatment duration (10 to 20 years): HR 0.71, 95% CI 0.59 to 0.86 |

and up to 19 years assessed with: Not including incident CRC cases at earlier periods follow-up: range 10 years to 19 years		High <sup>d,e,h,l,m</sup>	0.79)	2,149 per 100,000 <sup>n</sup>	<b>763 fewer per 100,000</b> (1,020 fewer to 444 fewer)
Cardiovascular event: major CVD events at 3- 10 years assessed with: nonfatal MI, nonfatal stroke, CVD mortality follow-up: range 3.6 years to 10.1 years	134470 (11 RCTs) <sup>1,10,11,12,13,14,15,3,7,8,9,b,c,j</sup>	⊕⊕⊕⊕ High <sup>d,e,o,p,q</sup>	OR 0.90 (0.85 to 0.95)	Estimated risk at 20-year timeframe	
				5,000 per 100,000 <sup>r</sup>	<b>477 fewer per 100,000</b> (718 fewer to 238 fewer)
				Estimated risk at 20-year timeframe	
				20,000 per 100,000 <sup>r</sup>	<b>1,633 fewer per 100,000</b> (2,474 fewer to 808 fewer)

1. WHS trial, . . . A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women.N Engl J Med; 2005.
2. BMD trial, . Randomised trial of prophylactic daily aspirin in British male doctors.Br Med J (Clin Res Ed); 1988.
3. TPT trial, . Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk.Lancet; 1998.
4. SALT trial, . Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group.Lancet; 1991.
5. UK-TIA trial, . The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results.J Neurol Neurosurg Psychiatry; 1991.
6. PHS trial, . Low-dose aspirin and incidence of colorectal tumors in a randomized trial.Natl Cancer Inst; 1993.
7. JPPP trial, . Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial.JAMA; 2014.
8. ASCEND trial, . Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus.N Engl J Med; 2018.

- Long treatment duration (> 20 years): HR 0.67, 95% CI 0.55 to 0.82).

The critical outcomes showing desirable effects were: death from colorectal cancer, diagnosis of colorectal cancer, and cardiovascular events.

#### Decision thresholds

#### CRC mortality:

- Trivial/Small: 35 per 100,000
- Small/Moderate: 95 per 100,000
- Moderate/Large: 175 per 100,000

#### CRC incidence:

- Trivial/Small: 75 per 100,000
- Small/Moderate: 200 per 100,000
- Moderate/Large: 375 per 100,000

#### Major CVD events including CVD mortality:

- Trivial/Small: 60 per 100,000
- Small/Moderate: 162 per 100,000
- Moderate/Large: 298 per 100,000

#### All cause mortality:

While this outcome was not prioritized as a critical outcome for decision-making, it was considered as an additional endpoint.

Evidence from a large systematic review on adults using low-dose aspirin for the primary prevention of cardiovascular disease was conducted for the US Preventive Services Task Force (USPSTF). This SR pooled 11 randomised controlled trials on low-

9. JPAD trial, . Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial.JAMA; 2009.
  10. AAA trial, . Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial.JAMA; 2010.
  11. POPADAD trial, . The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease.BMJ; 2008.
  12. PPP trial, . Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general Practice.Lancet; 2001.
  13. HOT trial, . Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.Lancet; 1998.
  14. ARRIVE trial, . Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial.Lancet; 2018.
  15. ASPREE trial, . Effect of Aspirin on Cancer Incidence and Mortality in Older Adults.J Natl Cancer Inst; 2021.
- a) The WHS data was provided by the WHS team via personal communication to the USPTF review team (Guirguis-Blake 2022).
  - b) Based on the systematic review: Guirguis-Blake JM, et al. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: An Evidence Update for the U.S. Preventive Services Task Force Evidence Synthesis No. 211. AHRQ Publication No. 21-05283-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2022.
  - c) Outcomes measured during the trial phase.
  - d) The USPTF assessed the methodological quality of the included studies with similar domains to the Cochrane risk of bias tool. Each study was assigned a quality rating of good, fair, or poor. Studies rated as poor quality were not eligible for the review. Therefore, we did not downgrade the certainty of the evidence due to the risk of bias.
  - e) I2: 0%
  - f) We did not downgrade for indirectness. The mean age of the included participants ranged from 54 to 67 years. The duration of aspirin use was generally short, ranging from 3 to 10 years. In all the studies, but the WHS trial, the mean aspirin duration ranged from 3 to 7 years. The daily dose of aspirin was high in the BMD trial (500 mg) and UK-TIA (300 or 1200 mg). The mean follow-up from 17.5 to 18.3 years. 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).
  - g) Downgraded two levels for imprecision. The point estimate of the absolute risk difference points to small benefit. However, it crosses 2 thresholds (small/moderate, moderate/large benefit).
  - h) We could not assess the risk of publication bias due to the insufficient number of studies per meta-analysis (less than eleven).
  - i) We estimated the control risk (CR), also known as cumulative risk in the 50-69 age group at 20-

dose aspirin including approximately 134,000 participants and found no clear effect on all-cause mortality (OR 0.98, 95% CI 0.93–1.03). Overall, the certainty of evidence was rated as high, reflecting consistent findings across trials and a precise estimate centered on no important benefit or harm. The USPSTF review also noted that ASPREE was the only individual trial to report a statistically significant increase in mortality among older adults, suggesting that effects may differ in very elderly populations.

#### **All-cancer mortality:**

While this outcome was not prioritized as a critical outcome for decision-making, it was considered as an additional endpoint.

No systematic reviews of randomized controlled trials were identified that provide pooled estimates specifically for all-cancer mortality in the context of low-dose aspirin for primary prevention.

The WG discussed data from one recent observational study (2) reporting that long-term low-dose aspirin use was not associated with a reduction in overall cancer incidence (continuous use HR = 1.04, 95% CI 1.03–1.06). However, use for ≥5–10 years was associated with at least 10% lower hazard ratios (HR ≤ 0.90) for several site-specific cancers, including cancers of the colon, rectum, esophagus, stomach, liver, pancreas, and small intestine, as well as head and neck cancer, brain tumors and meningioma, melanoma, thyroid cancer, non-Hodgkin lymphoma, and leukemia. In contrast, increased risks were observed for lung and bladder cancer, with hazard ratios above 1. While discussing these estimates, the Working Group noted concerns about the methodological quality of this study, as the

years. First, we obtained the annual incidence rate (IR) of CRC mortality in the 50-69 age group (EU-27): 0.0335%. (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 20-year period (IRx20). Third, we converted the r to the CR (%) by using the formula  $CR = [1 - \exp(-r)] \times 100$ .

- j) We did not find serious limitations in the risk of bias assessment. However, we could not assess the risk of attrition bias and selective outcome reporting for WHS: the results were provided via personal communication to the USPTF team, and we did not find a prospective registration for this trial. Although it is unclear if these potential limitations will likely lower the confidence in estimating the effect, we decided not to downgrade for risk of bias.
- k) Based on observational follow-up after trial had ended.
- l) We did not downgrade for indirectness. The participants' mean age was consistently below 60 years. The duration of aspirin use was generally short, ranging from 4.4 to 10.1 years. In all the studies but the WHS trial (mean use of 10.1 years), the mean aspirin use duration was six years at the most. The follow-up ranged from 10 to 19 years. 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) We did not downgrade for imprecision. The point estimate of the absolute risk difference exceeds our predefined threshold and points to large benefit. The CI 95% does not cross the null and is always compatible with large benefit.
- n) We estimated the control risk (CR), also known as cumulative risk, in the 50-69 age group, at 20-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 20-year period (IRx20). Third, we converted the r to the CR (%) by using the formula  $CR = [1 - \exp(-r)] \times 100$ .
- o) We did not downgrade for indirectness. The participants' mean age ranged between 55 and 74 years. The duration of aspirin use (and follow-up) was generally short, ranging from 3.6 to 10.1 years. All the studies had low aspirin dosage, ranging between 75 and 100 mg daily (100 mg daily in 70%). 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).
- p) We did not downgrade for imprecision. The point estimate of the absolute risk difference exceeds our predefined threshold and points to a large benefit. The CI 95% is compatible with large benefits.
- q) Publication bias was not detected (Harbord test for small study effects  $p=0.61$ ).
- r) Baseline risk at 20 years for low-risk and moderate-risk of developing CVD events including CVD mortality were extrapolated based on the FRAMINGHAM score.

statistical analysis did not adjust for key confounders (e.g., smoking status).

The ECICC WG agreed on the judgment of 'large' regarding desirable effects.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

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Aspirin was associated with a reduced risk of renal disease progression (HR 0.27 [95% CI 0.08–0.96] after adjustment for age, baseline eGFR, and diabetes; HR 0.36 [95% CI 0.10–1.33] after further adjustment for albuminuria).</li> <li>• In another trial (ASPREE trial), over a median follow-up of 4.7 years, the annual decline in eGFR was nearly identical between groups (–0.97 vs –0.99 ml /min/1.73 m<sup>2</sup>), indicating no clinically</li> </ul> </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 low-dose aspirin	Risk difference with Low-dose aspirin	Major gastrointestinal bleeding at 1- 10 years follow-up: range 1 years to 10.1 years	119130 (10 RCTs) <sup>1,10,2,3,4,5,6,7,8,9,a,b,c</sup>	⊕⊕⊕⊕ High <sup>d,e,f,g,h</sup>	OR 1.58 (1.38 to 1.80)	Estimated risk at 20-year follow up						180 per 100,000	<b>104 more per 100,000</b> (68 more to 144 more)	Gastrointestinal ulcer at 10 years follow-up: mean 10.1 years since the intervention start	39876 (1 RCT) <sup>9,c</sup>	⊕⊕○○○ Low <sup>h,i,j,k</sup>	HR 1.17 (1.09 to 1.26)	Estimated risk at 20-year follow up						1,990 per 100,000	<b>334 more per 100,000</b> (177 more to 511 more)	Chronic kidney disease	0 (2 RCTs) <sup>11,12,c</sup>	⊕○○○○ Very low <sup>l,m</sup>	-	Two separate randomised trials evaluated the effects of aspirin on kidney function. <ul style="list-style-type: none"> <li>• In the AASER trial (Goicoechea et al., 2018), renal disease progression occurred in 6.0% of participants receiving aspirin versus 27.9% receiving standard therapy. 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Thus, the WG judged that they are not considered within the scope of outcome of major Gastrointestinal (GI) bleeding.</p> <p><b>Decision thresholds</b></p> <p><b>Major GI bleeding:</b></p> <ul style="list-style-type: none"> <li>• Trivial/Small: 175 per 100,000</li> <li>• Small/Moderate: 550 per 100,000</li> <li>• Moderate/Large: 950 per 100,000</li> </ul> <p><b>GI ulcer</b> (considered to cause half the burden of GI perforation, see <a href="#">here</a>):</p> <ul style="list-style-type: none"> <li>• Trivial/Small: 250 per 100,000</li> <li>• Small/Moderate: 900 per 100,000</li> <li>• Moderate/Large: 1550 per 100,000</li> </ul> <p>The ECICC WG agreed on the judgment of 'small' regarding undesirable effects.</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 low-dose aspirin	Risk difference with Low-dose aspirin																																							
Major gastrointestinal bleeding at 1- 10 years follow-up: range 1 years to 10.1 years	119130 (10 RCTs) <sup>1,10,2,3,4,5,6,7,8,9,a,b,c</sup>	⊕⊕⊕⊕ High <sup>d,e,f,g,h</sup>	OR 1.58 (1.38 to 1.80)	Estimated risk at 20-year follow up																																								
				180 per 100,000	<b>104 more per 100,000</b> (68 more to 144 more)																																							
Gastrointestinal ulcer at 10 years follow-up: mean 10.1 years since the intervention start	39876 (1 RCT) <sup>9,c</sup>	⊕⊕○○○ Low <sup>h,i,j,k</sup>	HR 1.17 (1.09 to 1.26)	Estimated risk at 20-year follow up																																								
				1,990 per 100,000	<b>334 more per 100,000</b> (177 more to 511 more)																																							
Chronic kidney disease	0 (2 RCTs) <sup>11,12,c</sup>	⊕○○○○ Very low <sup>l,m</sup>	-	Two separate randomised trials evaluated the effects of aspirin on kidney function. <ul style="list-style-type: none"> <li>• In the AASER trial (Goicoechea et al., 2018), renal disease progression occurred in 6.0% of participants receiving aspirin versus 27.9% receiving standard therapy. Aspirin was associated with a reduced risk of renal disease progression (HR 0.27 [95% CI 0.08–0.96] after adjustment for age, baseline eGFR, and diabetes; HR 0.36 [95% CI 0.10–1.33] after further adjustment for albuminuria).</li> <li>• In another trial (ASPREE trial), over a median follow-up of 4.7 years, the annual decline in eGFR was nearly identical between groups (–0.97 vs –0.99 ml /min/1.73 m<sup>2</sup>), indicating no clinically</li> </ul>																																								

				meaningful difference.	
Intra-cranial hemorrhage	134470 (11 RCTs) <sup>1,13,14,2,3,4,5,6,7,8,9,n,o</sup>	⊕⊕⊕⊕ High	<b>OR 1.31</b> (1.11 to 1.54)	Study population	
				360 per 100,000	<b>111 more per 100,000</b> (39 more to 193 more)

1. ASCEND trial, . Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus.N Engl J Med; 2018.
2. JPAD trial, . Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial.JAMA; 2009.
3. AAA trial, . Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial.JAMA; 2010.
4. PPP trial, . Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general Practice.Lancet; 2001.
5. HOT trial, . Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.Lancet; 1998.
6. TPT trial, . Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk.Lancet; 1998.
7. ARRIVE trial, . Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial.Lancet; 2018.
8. ASPREE trial, . Effect of Aspirin on Cancer Incidence and Mortality in Older Adults.J Natl Cancer Inst; 2021.
9. WHS trial, , , . A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women.N Engl J Med; 2005.
10. ASPREE pilot, . Adverse effects of low-dose aspirin in a healthy elderly population.Clin Pharmacol Ther; 1993.
11. McNeill, JJ, Wolfe, R. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly.N Engl J Med; 2018.
12. Goicoechea, M, de Vinuesa, SG, Quiroga, B. Aspirin for primary prevention of cardiovascular disease and renal disease progression in chronic kidney disease patients: a multicenter randomized clinical trial (AASER Study)..J Thromb Haemost; 2018.
13. JPPP trial, . Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial.JAMA; 2014.
14. POPADAD trial, . The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease.BMJ; 2008.

- a) Mean ages from 54 to 75 years. Aspirin daily use: 50 or 100 mg. Mean duration of aspirin use: 4.7 to 10.3 years.
- b) Based on the systematic review: Guirguis-Blake JM, et al. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: An Evidence Update for the U.S. Preventive Services Task Force Evidence Synthesis No. 211. AHRQ Publication No. 21-05283-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2022.
- c) Outcomes measured during the trial phase.
- d) The USPSTF assessed the methodological quality of the included studies with similar domains to the Cochrane risk of bias tool. Each study was assigned a quality rating of good, fair, or poor. Studies rated as poor quality were not eligible for the review. Therefore, we did not downgrade the certainty of the evidence due to the risk of bias.
- e) I2: 25%
- f) We did not downgrade for indirectness. The participants' mean age ranged between 55 and 74 years. The duration of aspirin use (and follow-up) was generally short, ranging from 1 to 10.1 years. All the studies had low aspirin dosage, ranging between 75 and 100 mg daily. 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).
- g) We did not downgrade for imprecision because the CI 95% does not cross the null value and is compatible with trivial harm.
- h) We could not assess the risk of publication bias due to the insufficient number of studies per meta-analysis (less than eleven).
- i) All the information based on a study at an unclear risk of bias
- j) We did not downgrade for indirectness. The participants' mean age in the WHS was 54 years (the study only included women). Aspirin daily dose: 50 mg. Mean aspirin use: 10.1 years. Follow-up: trial phase. 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).
- k) Downgraded one level for imprecision. The point estimate of the absolute risk difference points to trivial harm. However, it crosses 1 threshold (trivial/small harm).
- l) Downgrade one level due to: Patients, carers and people delivering the intervention were probably aware of the assigned interventions and an inappropriate analysis was made to estimate the adherence to the intervention.
- m) Downgraded by two levels as CI goes from 1439 fewer to 522 more cases in the study on renal disease progression
- n) Findings were consistent with other recent systematic reviews showing an increased risk of intracranial bleeding with low-dose aspirin. Huang et al. (2019) conducted a meta-analysis of primary-prevention RCTs assessing intracranial hemorrhage with aspirin  $\leq$ 100 mg/day. Most trials used 75–100 mg daily (one used 100 mg every other day), with follow-up ranging from approximately 2.3 to 8.2 years (HOT, PPP, AAA, JPPP, ASCEND, ASPREE). Aspirin increased the risk of intracranial hemorrhage (0.63% vs 0.46%; RR 1.37)
- o) This outcome is based on an analysis of randomized trials included in the USPSTF systematic review

	assessing intracranial bleeding (TPT, HOT, PPP, WHS, POPADAD, JPAD, AAA, ASCEND, JPPP, ARRIVE, ASPREE).	
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## Certainty of evidence

What is the overall certainty of the evidence of effects?

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

## 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"> <li>○ Important uncertainty or variability</li> <li>○ Possibly important uncertainty or variability</li> <li>● Probably no important uncertainty or variability</li> <li>○ No important uncertainty or variability</li> </ul>		<p>Trade-offs of disutility between non-fatal stroke (thrombotic or haemorrhagic) and Gastrointestinal 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>The Working Group voted on this judgement:</p> <ul style="list-style-type: none"> <li>● 4 members voted for possibly important uncertainty or variability</li> <li>● 5 members voted for probably no important uncertainty or variability</li> <li>● 1 member voted for no important uncertainty or variability</li> <li>● 1 member abstained</li> </ul>

Outcome	Research evidence	Interpretation of findings
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<b>Diagnosis of Colorectal Cancer (colorectal cancer incidence)</b>	<p>1 SR with 6 cross-sectional studies with patients with colorectal cancer<sup>(13-16)</sup> (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>
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<b>Death from colorectal cancer (colorectal cancer mortality)</b>	<p>1 SR with 13 quantitative<sup>(17-19)</sup> and three qualitative studies<sup>(20-22)</sup> 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>
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<b>Harms (major GI bleeding, GI perforation, GI ulcer)</b>	<p><b>Major GI bleeding</b></p> <p>Major GI bleeding (from major bleeding)</p> <p>1 SR<sup>(23)</sup> 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<sup>(24)</sup> 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><b>GI perforation</b></p> <p>1 SR with 2 qualitative studies<sup>(25, 26)</sup> 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><b>GI ulcer</b></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>
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<b>All severe stroke/including Haemorrhagic Stroke</b>	<p>1 SR<sup>(27)</sup> 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>
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<b>Cardiovascular Events</b>	<p>Includes Heart Failure, Arrhythmia, Myocardial Infarction, Transient Ischaemic Attack</p> <p><b>Chronic heart failure</b></p> <p>1 SR<sup>(28)</sup> 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><b>Arrhythmia</b></p> <p>1 SR<sup>(29)</sup> 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><b>Myocardial Infarction</b></p> <p>1 SR<sup>(30)</sup> 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><b>Transient ischaemic attack</b></p> <p>1 SR<sup>(31)</sup> 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>
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## 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"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>● Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		<p>The Working Group previously judged that the identified evidence suggested large benefits, small harms, low certainty of the evidence and probably no important uncertainty or variability.</p> <p>Long-term desirable consequences are observed in trials that followed study subjects for 10 to 18 years. After 10 years of Aspirin administration, small harms are observed.</p> <p>This, along with the fact that there might be uncertainty as to when exactly to start or stop (e.g., What happens then?) the intervention, led the Working Group to consider that the balance between desirable and undesirable effects probably favours the intervention.</p>

## Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Large costs</li> <li>○ Moderate costs</li> <li>● Negligible costs and savings</li> <li>○ Moderate savings</li> <li>○ Large savings</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>Drug unit costs extracted from the studies included in the cost-effectiveness review as follows:</p>	<p>The Working Group noted that the identified studies did not consider additional costs and savings (e.g., resources required for administration such as general practitioners' time and resources saved).</p> <p>The Working Group noted that Aspirin is available 'over the counter' in most settings and that, as a result, people may start taking Aspirin without a clinical consultation. However, for informed use of Aspirin, counselling may be required, e.g., because of co-interventions that patients receive.</p>

Study	Drug	Cost (currency, year)	Cost (€, 2022)*	Source
<b>Aspirin / No intervention</b>				
Ladabaum, 2001	Aspirin per person-year	US\$ 4 (1998)	€ 4.60	Retail cost at University of Michigan pharmacy, Ann Arbor, Michigan.
Suleiman, 2002	Annual aspirin prevention	US\$ 18 (NR)	€ 19.79	
Hassan, 2012	One year cost of daily administration of aspirin 75 mg	US\$ 3 (2010)	€ 2.75	Indiana University Medical Center Pharmacy, Indianapolis, Indiana, USA.
<b>Aspirin + CRC screening / CRC screening</b>				
Squires, 2011	Annual cost of aspirin (300 mg daily)	GBP 17.19 (2008)	€ 21.52	British National Formulary 57. ed. London: British Medical Association and Royal Pharmaceutical Society, 2008.

\* Cost Euro 2022: Harmonised Index of Consumer Prices (HICP, Eurostat) and Purchasing Power Parity (PPP Euro, Eurostat) for 2022 were used for adjustment

The patients in this target group may take several medicines simultaneously and, therefore, need to consider any risks and drug interactions arising from the concurrent use of Aspirin and various other medicines (herbal products and food supplements). Furthermore, individuals need to be aware of and inform physicians to avoid any impact on surgeries or other clinical procedures due to Aspirin administration.

Lastly, decision aids/supporting tools should be provided to individuals. These should present the risks and benefits of low-dose Aspirin.

## 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"> <li>○ Very low</li> <li>○ Low</li> <li>○ Moderate</li> <li>○ High</li> <li>● No included studies</li> </ul>	<p>Drug unit costs extracted from the studies included in the cost-effectiveness review. The evaluation of the certainty of the evidence does not apply.</p>	

## 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"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>○ Favors the intervention</li> <li>○ Varies</li> <li>● No included studies</li> </ul>	<p>The searches for research evidence were conducted on 15th October 2023 and 4 studies were found.</p>	<p>The panel considered that the studies retrieved [Hassan et al. (2012), Ladabaum et al. (2001), Suleiman et al. (2002) and Squires et al. (2011)] offer significant indirect evidence to assess the cost-effectiveness of the intervention because the assumptions and input variables were not consistent with the results of those of the Systematic Review on effectiveness.</p> <p>For instance, in Suleiman et al. (2002), the relative risk reduction of colorectal cancer is assumed to be 50%; but this diverges with the magnitude of the effect as seen under 'Desirable Effects'. Also, (a) Cardiovascular outcomes were not addressed, and (b) the certainty of the evidence is low to moderate (with all studies being observational).</p> <p>Other identified studies were excluded because they focused on secondary prevention. Thus, the Working Group did not consider these studies to inform the judgment.</p>

## Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ Reduced</li> <li>○ Probably reduced</li> <li>● Probably no impact</li> <li>○ Probably increased</li> <li>○ Increased</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>No systematic reviews were found related to equity of colorectal cancer prevention with aspirin or NSAIDs.</p>	<p>The Working Group noted that obtaining Aspirin without a prescription in some systems is possible, it is usually an 'out-of-pocket' expense, which might represent barriers to health equity.</p> <p>On the other hand, the panel believed that the possible impact on health equity would be minimal due to the low price of Aspirin and its accessibility.</p> <p>However, this may vary from country to country, given the differences in the respective healthcare</p>

systems.

Thus, overall, it is considered that it probably will not impact equity.

## Acceptability

Is the intervention acceptable to key interest-holders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS										
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input checked="" type="radio"/> Probably yes</li> <li><input type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<table border="1"> <thead> <tr> <th>Outcome</th> <th>Studies / No. of participants / Estimates</th> <th>Interpretation of findings</th> </tr> </thead> <tbody> <tr> <td><b>Adherence</b></td> <td>- 1 SR<sup>(1)</sup> 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">Indirect evidence suggests that the likelihood that eligible users of aspirin 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 aspirin.</td> </tr> <tr> <td><b>Persistence of use</b> Defined as the length of time between uptake and last dose</td> <td>- 1 SR<sup>(2)</sup> 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><b>Willingness to take</b></td> <td>- 1 SR<sup>(1)</sup> 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<sup>(2)</sup> 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><b>References</b>1. 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	<b>Adherence</b>	- 1 SR <sup>(1)</sup> 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). 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Perceptions of risk and benefit also influence decision-making and use.	<p>Based on the evidence presented, the Working Group deemed that initial adherence is high but might vary (decrease) over time, considering the long-term use of the drug.</p> <p>The panel also discussed that there are likely concerns for healthcare professionals because the intervention has not been widely recommended so far and because it possibly requires counselling. The Working Group noted that there was no evidence from the perspective of policymakers.</p> <p>The Working Group judged that the intervention was probably acceptable to key stakeholders.</p>
Outcome	Studies / No. of participants / Estimates	Interpretation of findings										
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## Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>● Probably yes</li> <li>○ Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>No systematic reviews were found related to feasibility of colorectal cancer prevention with aspirin or NSAIDs.</p>	<p>The Working Group voted on this judgement with the following results:</p> <ul style="list-style-type: none"> <li>● 5 members voted probably yes</li> <li>● 1 member voted yes</li> <li>● 1 member voted probably no</li> <li>● 1 member voted varies</li> <li>● 2 members abstained</li> </ul> <p>The ECICC Working Group agreed on the judgment 'probably yes'.</p>

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## SUMMARY OF JUDGEMENTS

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

### Recommendation

For asymptomatic adults aged 50 to 70 with average risk of colorectal cancer, the ECICC Working Group (WG) suggests using low-dose aspirin for at least 10 years for primary prevention of colorectal cancer (conditional recommendation, low certainty of the evidence).

### Remarks:

The Working Group agreed that the target age range of the population for this recommendation is 50 to 70, which is in accordance with the trials.

Given that the benefit is expected to be long-term, individuals at the lower end of the age range (i.e., younger individuals) will likely benefit more from Aspirin use. The later in life an individual starts taking Aspirin, the fewer benefits there will be. Fewer cardiovascular events were observed in patients taking Aspirin for at least 10 years. However, there are small undesirable effects which may appear at any time during Aspirin treatment.

To make well-informed decisions, average-risk individuals in this age range should be informed about the benefits and risks, particularly potential risk factors that increase the probability of harm, such as bleeding and ulcers.

The Working Group noted that a decision support tool and/or consultation with a physician/pharmacist are needed. Also, the decision support tool must emphasise that the expected benefits of Aspirin administration will appear over the long term. Similarly, harms may occur immediately/in the short term.

The Working Group concluded that individuals who place a high value on the prevention of colorectal cancer will be more likely to use Aspirin, while those placing a high value on preventing bleeds or other harms may not. People at higher risk of CVD are likely to achieve more benefits, and prevention of CRC is an additional benefit. Colorectal cancer risk reduction is an additional benefit for those already taking it long-term.

Lastly, the Working group defined the intervention as a low dose of Aspirin, which is proxied by 75-100 mg (a similar dose to that used in the reviewed trials).

## Justification

### Overall justification

The recommendation to use low-dose Aspirin in adults aged 50 to 70 years at average risk for primary prevention of colorectal cancer for at least 10 years is based on a balance of benefits and risks, with a conditional recommendation due to low certainty of evidence. Low-dose Aspirin (75-100 mg) is widely accessible in the EU Member States, has negligible costs, and is likely to be acceptable to patients and healthcare providers. There is minimal uncertainty in patient values, as cancer prevention is a common priority in this population. However, the low certainty of evidence supporting the intervention necessitates shared decision-making to tailor the recommendation to individual circumstances. This approach reflects a cautious stance, ensuring potential benefits outweigh risks while addressing variability in patient preferences and risk factors.

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

- 7 members voted for a conditional in favour of the intervention
- 1 member voted for a conditional for either the intervention or comparison
- 2 members abstained

### Detailed justification

#### *Desirable Effects*

The Working Group considered the benefits to be large.

#### *Undesirable Effects*

The Working Group considered the harms to be small.

#### *Certainty of evidence*

The overall certainty was rated as low.

#### *Balance of effects*

On balance, and considering the long-term benefits, the Working Group judged there may be more benefits than harms.

## Subgroup considerations

The benefits of using Aspirin are long-term and expected to be higher in those who start at the younger age of the 50- to 70-year-old age group. The reviewed studies have shown that starting Aspirin at an older age was not associated with a lower risk of colorectal cancer.

The evidence suggests that there is an association between cardiovascular disease (e.g., myocardial infarction, ischaemic stroke and transient ischaemic attack) and long-term low-dose Aspirin use. Moreover, people at higher baseline risk of cardiovascular diseases taking Aspirin are likely to achieve higher absolute benefits (in terms of cardiovascular risk reduction). This may reflect an additional benefit for people between the ages of 50-70 aiming to prevent colorectal cancer.

This recommendation may not apply to people who are already taking antiplatelet agents or anticoagulants for other reasons, nor to those with an elevated bleeding risk (e.g., a

prior history of gastrointestinal bleeding or ulcers), because they are at greater risk of harm.

### Implementation considerations

Resources are required to implement the recommendation, e.g., clinician consultation and decision aids/supporting tools, which need to be provided.

To follow this recommendation, people should be fully informed and shared decision-making (between clinician and patient) will be required. The side effects of Aspirin use need to be monitored, and the possible health harms need to be considered against its desirable effects. Furthermore, other factors must be considered, such as any existing gastrointestinal ulcers, concurrent use of anticoagulants, and renal impairment.

In addition, the risk for cardiovascular disease needs to be considered.

This recommendation applies to people 50 to 70 years of age and not beyond.

Regarding the potential interruption of Aspirin for any surgical or medical procedures, and the use of gastroprotectants medications (i.e. proton pump inhibitors) the Working Group suggests reviewing high-quality recommendations and guidelines from other organizations.

### Monitoring and evaluation

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

### Research priorities

#### Benefits and harms:

- The Working Group considered that additional observational studies (with a low risk of bias) with long term outcomes may be useful in confirming the benefits and harm estimates. This evidence could also inform about start and end ages for this recommendation, which is needed to evaluate if extrapolation to other age groups is warranted.
- Research on other potential harms from the long-term use of Aspirin is needed (well-organised registry studies).
- Research to establish the impact of Aspirin use on the accuracy of Fecal immunochemical test (FIT) based screening and its association with the site of possible lesions.
- Further research would be needed on which anatomic sites are targets of primary prevention practices. Some studies have shown the association between Aspirin use and the detection of CRC and adenomas, but not between Aspirin use and advanced serrated lesions.

**Values, resources and acceptability:**

- More information is needed about values regarding the longer-term outcomes of interest. Furthermore, information on the patients' acceptability to use Aspirin long-term would be useful.
- Cost-effectiveness analyses using the estimates of effect used in this EtD and including information about counselling, would be beneficial.

**Implementation:**

- Research about the communication and use of information in prevention interventions like this one will be helpful in understanding optimal ways of shared decision-making and counselling in this context.
- The role of aspirin in prevention of CRC in the context of effective screening programmes should further explored.

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## REFERENCES SUMMARY

1. JRC, . Colorectal cancer factsheet JRC 2021.Joint Research Centre; 2021.
2. Skriver, C. Long-term aspirin use and cancer risk: a 20-year cohort study.J Natl Cancer Inst; 2024.

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