IJC Heart & Vasculature 36 (2021) 100851

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Public health impact of low-dose aspirin on colorectal cancer, cardiovascular disease and safety in the UK – Results from micro-simulation model ☆

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ARTICLE INFO

Article history:
Received 19 July 2021
Accepted 26 July 2021

Keywords:
Aspirin
Cardiovascular disease
Colorectal cancer
Safety
Computer simulation
Epidemiology
Risk factors

ABSTRACT

Background: Low-dose aspirin therapy reduces the risk of cardiovascular disease and may have a positive effect on the prevention of colorectal cancer. We evaluated the population-level expected effect of regular low-dose aspirin use on cardiovascular disease (CVD), colorectal cancer (CRC), gastrointestinal bleeding, symptomatic peptic ulcers, and intracranial hemorrhage, using a microsimulation study design.
Methods: We used individual-level state transition modeling to assess the impact of aspirin in populations aged 50–59 or 60–69 years old indicated for low-dose aspirin usage for primary or secondary CVD prevention. Model parameters were based on data from governmental agencies from the UK or recent publications.
Results: In the 50–59 years cohort, a decrease in incidence rates (IRs per 100 000 person years) of non-fatal CVD (-203 and −794) and fatal CVD (-97 and-381) was reported in the primary and secondary CVD prevention setting, respectively. The IR reduction of CRC (-96 and −93) was similar for primary and secondary CVD prevention. The IR increase of non-fatal (116 and 119) and fatal safety events (6 and 6) was similar for primary and secondary CVD prevention. Similar results were obtained for the 60–69 years cohort.
Conclusions: The decrease in fatal CVD and CRC events was larger than the increase in fatal safety events and this difference was more pronounced when low-dose aspirin was used for secondary compared to primary CVD prevention. These results provide a comprehensive image of the expected effect of regular low-dose aspirin therapy in a UK population indicated to use aspirin for CVD prevention.

1. Introduction

Low-dose aspirin therapy reduces the risk of cardiovascular disease (CVD, particularly myocardial infarction and ischemic stroke) among patients at high risk of developing CVD (primary CVD prevention) [1], as well as among patients who have already experienced one or more CVD events (secondary CVD prevention) [2].

There is emerging evidence that aspirin also has a positive effect on the prevention of colorectal cancer (CRC). In a *meta*-analysis of four randomized controlled trials (RCTs) of 14,033 subjects, regular use of low-dose aspirin (75–300 mg/day) led to substantial reductions in the 20-year incidence of colon cancer [3]. Additionally, a *meta*-analysis of observational studies showed that among regular low-dose aspirin users (75–100 mg), the CRC risk was reduced and this reduction could be observed after a treatment period of one year [4].

However, low-dose aspirin use is also associated with adverse effects, such as gastrointestinal (GI) bleeding, symptomatic peptic

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Preliminary results of this study have been presented as a poster at the 2019 International Conference on Pharmacoepidemiology & Therapeutic Risk Management and the 2020 European Society of Cardiology Congress.

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https://doi.org/10.1016/j.ijcha.2021.100851
2352-9067/

ulcers, and a rare but more severe event, intracranial hemorrhage (ICH). These adverse effects vary by dose and duration of aspirin use. In *meta*-analyses of RCTs and observational studies, low-dose aspirin treatment was associated with an increased relative risk for major GI bleeding and ICH, [5,6] however, a large observational study did not find a significantly increased risk of ICH due to low-dose aspirin usage [7].

Therefore, the benefits and risks of low-dose aspirin need to be considered together. The benefits of low-dose aspirin for secondary CVD prevention are generally considered to outweigh the risk while this remains up for debate in the primary CVD prevention setting [8]. The United States Preventive Service Task Force (USPSTF) 2016 recommendations include initiation of low-dose aspirin for primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10-year risk of developing CVD $\geq$ 10%, are not at increased risk for bleeding and have a life expectancy of at least 10 years, whereas the decision to initiate low-dose aspirin use in adults aged 60 to 69 years should be an individual one [9]. In Europe, initiating low-dose aspirin is recommended for secondary CVD prevention and in some European countries also for primary CVD prevention [10,11].

The overall public health impact of using low-dose aspirin in terms of numbers of CVD and CRC events prevented, and bleeding events caused is lacking in most studies on low-dose aspirin usage. Such information is especially sparse when considering European populations stratified by primary and secondary CVD prevention. This information is important because of the population-wide use of low-dose aspirin for both primary and secondary CVD prevention. Therefore, we used a micro-simulation model based on data representing the epidemiology in the UK, for which high-quality data was available, to evaluate the population-level expected benefits and risks of regular use of low-dose aspirin therapy. The model focused on adults eligible for low-dose aspirin treatment for primary prevention or secondary CVD prevention within the UK, accounting for the emerging evidence on the effect of aspirin for CRC prevention.

2. Methods

2.1. Model description

An individual-level state transition model based on a multi-state model [12] was used to simulate the impact of regular low-dose aspirin use (75–150 mg/day) on CRC, CVD, severe GI bleeding or symptomatic peptic ulcers requiring hospitalization, and ICH. The detailed methodology is described in the Supplemental Material Annex 1.

2.2. Population

The model was used to simulate individual event histories for hypothetical cohorts of 1 million adults aged 50–59 years and 1 million adults aged 60–69 years indicated to use low-dose aspirin for primary (i.e. with a higher than 10% 10-year risk of CVD, as calculated by the QRISK3 score) [13] or secondary CVD prevention. Subjects were followed from their start of follow-up till 20 years after the start of follow-up or death, whichever occurred first. Data on the QRISK3 score risk factors score was generated based on the descriptive statistics reported by Hippisley-Cox *et al.* [13] Baseline characteristics were assumed to remain constant during the full follow-up period except for age and CVD status.

2.3. ***Model parameters***

Information on the risks of the different events and the effect of low-dose aspirin on these risks was extracted from data sources selected by an extensive literature review. Priority was given to high-quality data reported by governmental organizations from the UK and large *meta*-analyses. The selected data-sources can be found in Table 1 and the search strategy can be found in the Supplemental Material Annex 1. Where necessary, the reported estimates were transformed into relative risks and yearly risks. Reports on the treatment duration necessary to observe an effect of low-dose aspirin on CRC have ranged from one year to over five years [3,22]. In the main analyses, the effect of low-dose aspirin on CRC was assumed to start after one year of treatment based on results from García Rodríguez *et al.* [22] as this study used validated exposure [30] and outcome [31] definitions to investigate the association between low-dose aspirin and colorectal cancer and was powered to detect an early effect. Subjects were assumed to discontinue low-dose aspirin treatment when a safety event occurred. Additionally, 50% of the subjects were assumed to be at risk of discontinuing low-dose aspirin treatment following the discontinuation pattern reported in Martín-Merino *et al* [24]. Subjects who discontinued low-dose aspirin treatment were assumed to not resume treatment during the rest of the follow-up period.

2.4. Generated patient history data

For both age cohorts, we simulated event histories (CVD, CRC, deaths, safety events): once simulating events assuming the cohort initiated low-dose aspirin treatment and once assuming the cohort did not initiate low-dose aspirin treatment. By subtracting the number of events that occurred during the follow-up period when low-dose aspirin treatment was not initiated from the number of events when low-dose aspirin was initiated, the effect of low-dose aspirin effect was quantified. Comparing the number of events might not give the full picture in case the exposure of interest impacts life expectancy. Therefore, the results are also expressed based on changes in incidence rates (IR, per 100,000 person-years) due to low-dose aspirin initiation.

Monte Carlo (MC) simulation reflecting input parameter uncertainty was used to generate 95% uncertainty intervals (UIs) of the model results.

2.5. Scenario and sensitivity analyses

The impact of two aspects of the model, the treatment duration required to observe the CRC effect and the number of subjects at risk of discontinuation were explored through scenario analyses. The minimal duration of low-dose aspirin use required before the effect on CRC is observed was varied between one, three, and five years [3,22]. Similarly, the percentage of subjects at risk for discontinuing low-dose aspirin treatment not caused by a safety event was varied between 0%, 50%, and 100%.

The impact of parameter uncertainty was investigated by use of a sensitivity analysis, varying the central value of each input parameter distribution one-at-a-time within a reasonable range of its uncertainty distribution (lower-limit of the 95% confidence interval (CI), mean estimate, upper-limit of the 95% CI) while keeping the other parameters constant.

This study was conducted following the International Society of Pharmacoepidemiology Guidelines for Good Pharmacoepidemiological Practices [32] and the International Society for Pharmacoeco-

Table 1
UK individual-level state transition model: evidence to build simulation model.

Model input	Evidence	Ref.
Cohort characteristics		
Primary CVD prevention	To evaluate the CVD risk, the UK NICE guideline recommends the utilization of the QRISK3 tool.	NICE, 2018 [14]
	The main risk factors included in the QRISK3 tool that are also risk factors for CRC are age, sex, smoking status, diabetes status and BMI next to measures such as cholesterol and systolic blood pressure.	Hippisley-Cox, 2017 [13]
	To simulate a population at increased CVD risk, the QRISK 3 algorithm is used.	
Secondary CVD prevention	The prevalence of CVD is estimated to be around 11.4% in the UK (all ages, both sexes). 7 million people living with CVD in the UK.	Global Burden of Disease database – 2017 data [15]
	The risk of developing a second CVD event depends on age, gender, diabetes, smoking status and BMI	Antithrombotic Trialists' (ATT) Collaboration, 2009 (web appendix) [2]
CRC screening	In the UK, the fecal occult blood test (home testing kit) and the bowel scope screening (flexible sigmoidoscopy) are used as part of the NHS Bower Screening program.	NHS website [16]
	In the UK, around half (50–58%) of people who are invited for bowel cancer screening are screened adequately within 6 months of invitation (uptake) and also half (50–58%) of eligible people are screened adequately (coverage).	Cancer research UK [17]
Baseline risks (and related mortality)		
CVD and related mortality	The CVD risk at baseline (at start of follow-up), will be calculated using the QRISK3 tool. The CVD risk will be re-calculated with increasing age.	Hippisley-Cox, 2017 [13]
	CVD case fatality in relation to predicted CVD risk	2016 European Guidelines on cardiovascular disease prevention in clinical practice [10]
CRC and related mortality	The most recent age- and sex-specific CRC incidence rates (2013–2015) from the Cancer Research UK statistics will be used.	Cancer research UK [18]
	The age- and sex-specific CRC related mortality (2013–2015) will also be obtained from the Cancer Research UK statistics.	Cancer research UK [19]
	CRC risk factors that are also associated with increased CVD risk (e.g. BMI, smoking, diabetes) will be accounted for.	Johnson, 2013 [20]
Severe GI bleeding	Age- and sex-specific baseline rates of severe GI bleeding requiring hospitalization will be obtained.	Thorat, 2015 [21]
	The rates of fatal GI complications show a strong and consistent effect of age, which will also be accounted for.	
ICH	Age- and sex-specific baseline rates of any ICH bleeding will be obtained.	Gaist D., 2013 [28]
Severe symptomatic peptic ulcers	Age- and sex specific baseline rates of severe symptomatic peptic ulcers requiring hospitalizations will be obtained	Thorat, 2015 [21]
	Case fatality after symptomatic peptic ulcers show a consistent effect of age and gender	
Other cause mortality	Mortality data will be obtained from Human Mortality Database)	Human Mortality Database [29]
Effects of low-dose aspirin use (benefits)		
Primary CVD prevention	Aspirin use was associated with significant reductions in the composite cardiovascular outcome (cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke) compared with no aspirin (57.1 per 10 000 participant-years with aspirin and 61.4 per 10 000 participant-years with no aspirin) (hazard ratio [HR], 0.89 [95 %credible interval, 0.84–0.95]; absolute risk reduction, 0.38%[95 %CI, 0.20%-0.55%]; number needed to treat, 265)	Zheng, 2019 [1]
Secondary CVD prevention	In the secondary CVD prevention trials, aspirin allocation yielded a greater absolute reduction in serious vascular events (6·7% vs 8·2% per year, p < 0.0001).	Antithrombotic Trialists' (ATT) Collaboration, 2009 [2]
CRC (3 years)	Allocation to aspirin reduced the 20-year risk of colon cancer (incidence hazard ratio [HR] 0·76, 0·60–0·96, p = 0·02; mortality HR 0·65, 0·48–0·88, p = 0·005), but not rectal cancer (0·90, 0·63–1·30, p = 0·58; 0·80, 0·50–1·28, p = 0·35).	Rothwell, 2010 [3]
	Benefit increased with scheduled duration of treatment, such that allocation to aspirin of 5 years or longer reduced risk of proximal colon cancer by about 70% (0·35, 0·20–0·63; 0·24, 0·11–0·52; both p < 0·0001) and also reduced risk of rectal cancer (0·58, 0·36–0·92, p = 0·02; 0·47, 0·26–0·87, p = 0·01).	
CRC (1 year)	A reduction in CRC risk was seen throughout treatment duration, with a constant 40% reduction after the first year.	Garcia Rodriguez, 2017 [22]
Effects of low-dose aspirin use (risks)		
GI bleeding	The risk of excess GI bleeding depends on age and sex.	García Rodríguez, 2016 [6]
	The incidence of all GI bleeding events with low-dose aspirin varied between 0.5 and 3.6 cases per 1000 person-years.	
Proton pump inhibitor use	The use of proton-pump inhibitors (PPI) reduces the risk of GI bleeding due to aspirin use and this effect modifier will be accounted for.	Garcia Rodriguez 2018 UEGW abstract/ oral presentation [23]
	Among low-dose aspirin users concomitant use of PPI has been reported to be 32.6%	Personal communication with Luis Garcia Rodriguez
ICH	The risk of ICH associated to low-dose aspirin use is controversial in the literature.	García Rodríguez, 2016 [6]
	ICH is currently an identified risk in the Risk Management Plan. In the model we take a conservative approach and used the effects reported in a large *meta*-analysis	
Symptomatic peptic ulcers	history of peptic ulcer was associated with a significant increase in the risk of UGIB	Thorat, 2015 [21]

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Table 1 (*continued*)

Model input	Evidence	Ref.
Cessation of aspirin use		
Primary CVD prevention	Effect was assumed to be similar to the effect of cessation of low-dose aspirin for secondary prevention	
Secondary CVD prevention	This corresponds to five extra coronary events and three extra cerebrovascular events attributed to the discontinuation of ASA therapy among 1,000 patients on ASA during the first year of follow-up	Cea Soriano, 2013 [27]
Discontinuation pattern	The rate of discontinuation of ASA therapy was higher in the first year of therapy than in subsequent years (incidence of 26.7 per 100 person-years in the first year [95% CI: 26.1–27.3] versus 6.8 per 100 person-years in all subsequent years [95% CI: 6.6–7.0]).	Martín-Merino, 2012 [24]
Effect of screening		
	The CRC incidence was reduced by 26% using flexible sigmoidoscopy but no statistically significant difference in incidence of CRC with gFOB	Scholefield, 2012 [25]
	CRC mortality reductions are 13% through biennial gFOB screening and 30% with flexible sigmoidoscopy screening.	Atkin, 2017 [26]

nomics and Outcomes Research guidelines for the conduct of state-transition modeling [12].

3. Results

3.1. Participants and descriptive data

For one simulation run of each of the two age-specific cohorts (follow-up started between 50 and 59 or 60–69 years), the baseline patient characteristics are summarized (Table 2). Notably, in the cohort with follow-up started at 60–69 years, fewer additional risk factors were present than in the cohort where follow-up started at 50–59 years. This can be explained by the fact that age is a strong driver of CVD risk, hence, for the 10-year CVD risk to be > 10% fewer additional risk factors had to be present in the older cohort.

3.2. Number of events by indication (primary and secondary CVD prevention)

The change in the number of observed events during the 20-year follow-up period stratified by the indication for treatment can be found in Table 3 (cohort 50–59 years of age) and Table 4 (cohort 60–69 years of age).

In the younger cohort, a decrease in the total number of fatal events of −18,546 (95% UI −23,995 to −12,924) and −38,938 (95% UI −49,272 to −27,655) fatal events was observed when low-dose aspirin treatment was initiated for primary and secondary CVD prevention, respectively. More particularly, among subjects indicated for low-dose aspirin usage for primary CVD prevention a decrease of −30,258 (95% UI, −41,941 to −16,930) non-fatal CVD events, −14,688 (95% UI, −24,487 to −5,9923) non-fatal CRC events, and −21,689 (95% UI, −27,889 to −15,360) fatal CRC or CVD events was observed. Additionally, an increase of 20,439 (95% UI, 13,313 to 28,299) non-fatal safety events and 1,093 (95% UI, 519 to 1,733) fatal safety events was observed. Among subjects indicated for low-dose aspirin usage for secondary CVD prevention a decrease of −85,961 (95% UI, −109,401 to −58,031) non-fatal CVD events, −5,524 (95% UI −9,507 to −2,238) non-fatal CRC events, and −45,924 (95% UI, −58,630 to −32,743) fatal CRC or CVD events was observed. On the other hand, an increase of 19,897 (95% UI, 13,514 to 26,902) non-fatal safety events and 1,106 (95% UI, 472 to 1,893) fatal safety events was observed.

In the older cohort, a decrease in the total number of fatal events of −20,548 (95% UI −20,548 to −10,980) and −28,485 (95% UI −38,887 to −19,882) fatal events was observed when low-dose aspirin treatment was initiated for primary and secondary CVD prevention, respectively. Additionally, the reduction in the total number of CVD events was −42,054 (95% UI, −59,690 to −22,456) when the treatment was indicated for primary CVD prevention and −117,062 (95% UI, −168,274 to −75,876) CVD events when low-dose aspirin was initiated for secondary CVD prevention.

3.3. Incidence rates by indication (primary and secondary CVD prevention)

In the cohort of subjects for which the follow-up started between 50 and 59 years, the decrease in IRs of non-fatal CVD was −203 (95% UI, −277 to −115) when low-dose aspirin use was indicated for primary CVD prevention and −794 (95% UI, −997 to −536) when the treatment indication was for secondary CVD prevention (Table 3). Similar results were obtained for fatal CVD, with a change in IR of −97 (95% UI, −136 to −60) when low-dose aspirin use was indicated for primary CVD prevention and a change in IR of −381 (95% UI, −502 to −257) when low-dose aspirin use was indicated for secondary CVD prevention. Similar results were obtained for the cohorts in which the follow-up was started between 60 and 69 years (Table 4).

3.4. Scenario- and sensitivity analysis

Increasing the low-dose aspirin discontinuation decreased the impact of the low-dose aspirin effect on the benefits and risks (Supplemental Material Annex 2. Tables S2.1 and S2.2 and Figures S2.1 and S2.2). Changing the minimal duration of low-dose aspirin usage needed for observing the effect on CRC between one to five years only had a notable effect on the CRC events (Tables S2.5 and S2.6 and Figures S2.3 and S2.4). More particularly, the decrease in the IR of non-fatal CRC due to low-dose aspirin treatment was smaller when the necessary minimal treatment duration for observing an effect on CRC outcomes was increased. The effect of varying the minimal treatment duration on the IR of fatal CRC was less clear. Varying model parameters related to a specific outcome were varied mainly affected the related outcome while the effect on the other outcomes tended to be minimal. The sensitivity analysis also indicated that the conclusions hold over a range of reasonable parameter values (Figure S2.5 and S2.6). The scenario and sensitivity analyses are extensively described in Supplemental Material Annex 2.

4. Discussion

4.1. Key results

In this study, a simulation model was developed to predict the population-level expected benefits and risks associated with regular low-dose aspirin in subjects eligible to use low-dose aspirin for

Table 2
Baseline characteristics of two simulated cohorts eligible for low-dose aspirin for primary or secondary CVD prevention.

		Follow-up started at ages 50–59	Follow-up started at ages 60–69
Gender (%)	Female	107,039 (10.7)	298,400 (29.8)
	Male	892,961 (89.3)	701,600 (70.2)
Age (mean (SD))		55.70 (2.77)	64.74 (2.84)
Townsend score (mean (SD))		1.30 (3.29)	0.88 (3.28)
BMI (mean (SD))		26.00 (4.32)	25.84 (4.40)
Cholesterol to high density lipoprotein cholesterol ratio (mean (SD))		4.91 (1.23)	4.43 (1.22)
Systolic blood pressure (mmHG) (mean (SD))		134.43 (15.83)	130.08 (16.35)
Intraperson systolic blood pressure standard deviation (mmHg) (mean (SD))		11.56 (5.99)	10.97 (5.82)
Atrial fibrillation (%)	No	983,691 (98.4)	992,914 (99.3)
	Yes	16,309 (1.6)	7086 (0.7)
Rheumatoid arthritis (%)	No	991,430 (99.1)	991,320 (99.1)
	Yes	8570 (0.9)	8680 (0.9)
Atypical antipsychotic medication (%)	No	993,101 (99.3)	993,867 (99.4)
	Yes	6899 (0.7)	6133 (0.6)
Regular steroid tablet intake (%)	No	968,038 (96.8)	975,964 (97.6)
	Yes	31,962 (3.2)	24,036 (2.4)
Presence of migraines (%)	No	955,447 (95.5)	954,942 (95.5)
	Yes	44,553 (4.5)	45,058 (4.5)
Chronic kidney disease (stage 3, 4, or 5) (%)	No	992,202 (99.2)	995,086 (99.5)
	Yes	7798 (0.8)	4914 (0.5)
Severe mental illness (%)	No	940,379 (94.0)	940,325 (94.0)
	Yes	59,621 (6.0)	59,675 (6.0)
Systemic lupus erythematosus (%)	No	999,567 (100.0)	999,398 (99.9)
	Yes	433 (0.0)	602 (0.1)
Type 1 diabetes (%)	No	989,327 (98.9)	995,868 (99.6)
	Yes	10,673 (1.1)	4132 (0.4)
Type 2 diabetes (%)	No	958,151 (95.8)	979,054 (97.9)
	Yes	41,849 (4.2)	20,946 (2.1)
Family history of CVD (%)	No	828,997 (82.9)	881,645 (88.2)
	Yes	171,003 (17.1)	118,355 (11.8)
Treated hypertension (%)	No	929,658 (93.0)	944,517 (94.5)
	Yes	70,342 (7.0)	55,483 (5.5)
Diagnosis of erectile dysfunction or treatment for erectile dysfunction (%)	No	969,700 (97.0)	981,931 (98.2)
	Yes	30,300 (3.0)	18,069 (1.8)
Ethnicity (%)	White or not stated	888,232 (88.8)	901,904 (90.2)
	Indian	32,552 (3.3)	24,139 (2.4)
	Pakistani	24,009 (2.4)	14,285 (1.4)
	Bangladeshi	18,248 (1.8)	10,204 (1.0)
	Other Asian	13,066 (1.3)	13,060 (1.3)
	Black Caribbean	3479 (0.3)	5757 (0.6)
	Black African	6667 (0.7)	10,672 (1.1)
	Chinese	1719 (0.2)	3009 (0.3)
	Other ethnic group	12,028 (1.2)	16,970 (1.7)
Smoking status (%)	Non-smoker	282,967 (28.3)	457,114 (45.7)
	Former smoker	143,367 (14.3)	165,306 (16.5)
	Light smoker	281,500 (28.1)	205,644 (20.6)
	Moderate smoker	141,462 (14.1)	96,988 (9.7)
	Heavy smoker	150,704 (15.1)	74,948 (7.5)
10-year risk of CVD in subject eligible for low-dose aspirin for primary CVD prevention		14.5%	17.2%

The cohorts consisted of subjects between 50 and 59 or 60–69 years old at the start of the follow-up. Additional information on the exact definition of the covariates can be found in Hippisley-Cox et al., 2017.

primary or secondary CVD prevention in the UK. All simulation model parameters were informed by high-quality recent publications retrieved during a literature search. Several scenario analyses were performed; in all scenarios considered, low-dose aspirin initiation led to a decrease in the number of CRC and CVD events (fatal and non-fatal) and corresponding IRs. On the other hand, for GI bleedings, symptomatic peptic ulcers, and ICH the number of events and IRs increased with low-dose aspirin treatment. In general, the beneficial effect of low-dose aspirin treatment on fatal CVD and CRC outweighed the detrimental effect on the fatal safety outcomes. Similarly, a US microsimulation model showed that lifetime aspirin use for primary prevention initiated between ages 40–69 in persons with higher CVD risk has the potential for a positive net benefit, although this model did not include symptomatic peptic ulcers as a potential safety outcome [33].

Given the emerging evidence that aspirin has a preventive effect on colorectal cancer the perceived benefit-risk profile of low-dose aspirin usage for CVD prevention has changed. Taking into account the effect of prophylactic use of low-dose aspirin on CRC risk in addition to its effect on CVD, Cuzick *et al* reported a positive benefit-harm profile even in the general population [34]. This change in the benefit-risk profile is especially relevant when low-dose aspirin is used for primary CVD prevention where its effect on CVD is relatively moderate given the increase in safety events. In this study, both subjects indicated for low-dose aspirin treatment for primary and secondary CVD prevention were considered. Indication for primary or secondary CVD prevention had a large impact on the effect of low-dose aspirin on fatal and non-fatal CVD events. This is in line with the effects of low-dose aspirin on CVD in these two populations reported in the literature [1,2].

Table 3
Change in the number of events and incidence rate due to initiation of low-dose aspirin usage stratified by reason for treatment imitation in the 50–59 age group.

	Change in number of events (95% UI)		Change in incidence rate (95% UI)	
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention
Non-fatal CVD	−30258 (-41941, −16930)	−85962 (-109401, −58031)	−203 (-277, −115)	−794 (-997, −536)
Non-fatal CRC	−7868 (-12653, −3448)	−5525 (-9507, −2238)	−50 (-78, −22)	−49 (-79, −20)
Non-fatal GI bleeding	11,968 (4459, 19943)	11,828 (5380, 18768)	67 (24, 114)	69 (26, 115)
Non-fatal ICH	993 (337, 1624)	956 (356, 1648)	6 (2, 9)	6 (1, 11)
Non-fatal ulcer	7477 (7058, 7931)	7113 (6378, 8065)	43 (40, 45)	44 (39, 50)
Death, other causes	2049 (777, 3429)	5880 (3476, 8640)	3 (-4, 9)	8 (-5, 23)
Fatal CVD	−14549 (-20541, −8880)	−41307 (-55305, −27865)	−97 (-136, −60)	−381 (-502, −257)
Fatal CRC	−7140 (-10368, −4966)	−4618 (-7097, −2477)	−46 (-69, −31)	−44 (-67, −26)
Fatal GI bleeding	862 (212, 1501)	885 (280, 1578)	5 (1, 9)	5 (1, 10)
Fatal ICH	231 (64, 395)	221 (-11, 430)	1 (0, 2)	1 (0, 3)
Any fatal event	−18546 (-23995, −12924)	−38938 (-49272, −27655)	−135 (-178, −91)	−410 (-518, −282)
Any non-fatal event	−17687 (-33115, −2145)	−71590 (-100853, −44869)	−137 (-235, −37)	−724 (-952, −464)

The reported values were scaled in such a way that they can be interpreted as the change in the number of events per one million subjects followed for 20 years. Negative values correspond with a reduction in the number of events due to initiation of low-dose aspirin treatment, while positive values correspond with an increase due to the initiation of low-dose aspirin treatment. The low-dose aspirin effect on CRC was assumed to start after one year and 50% of the subjects were at risk for low-dose aspirin discontinuation not related to a safety event.

Table 4
Change in the number of events due to initiation of low-dose aspirin usage stratified by reason for treatment imitation in the 60–69 age group.

	Change in number of events (95% UI)		Change in incidence rate (95% UI)	
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention
Non-fatal CVD	−29115 (-41626, −15548)	−81075 (-116805, −52410)	−221 (-306, −125)	−796 (-1121, −534)
Non-fatal CRC	−8576 (-15129, −2474)	−6302 (-11584, −1726)	−60 (-105, −18)	−60 (-107, −18)
Non-fatal GI bleeding	19,759 (9516, 33063)	19,274 (9459, 31173)	123 (56, 210)	124 (54, 212)
Non-fatal ICH	1445 (684, 2342)	1410 (512, 2328)	9 (4, 15)	9 (3, 16)
Non-fatal ulcer	7945 (7365, 8441)	7542 (6576, 8468)	50 (46, 53)	50 (44, 56)
Death, other causes	5077 (3159, 7478)	11,934 (7357, 16658)	10 (-1, 22)	22 (-1, 46)
Fatal CVD	−12939 (-18064, −6907)	−35988 (-52235, −22140)	−98 (-135, −56)	−353 (-505, −225)
Fatal CRC	−9815 (-13055, −7063)	−6765 (-9524, −4193)	−71 (-99, −49)	−68 (-102, −42)
Fatal GI bleeding	1900 (915, 3378)	1914 (616, 3137)	12 (5, 21)	12 (3, 21)
Fatal ICH	423 (161, 690)	420 (113, 757)	3 (1, 4)	3 (0, 5)
Any fatal event	−15355 (-20548, −10980)	−28485 (-38887, −19882)	−144 (-197, −100)	−385 (-531, −265)
Any non-fatal event	−8542 (-28022, 10013)	−59149 (-95667, −29751)	−99 (−232, 31)	−673 (-1011, −404)

The reported values were scaled in such a way that they can be interpreted as the change in the number of events per one million subjects followed for 20 years. Negative values correspond with a reduction in the number of events due to initiation of low-dose aspirin treatment, while positive values correspond with an increase due to the initiation of low-dose aspirin treatment. The low-dose aspirin effect on CRC was assumed to start after one year and 50% of the subjects were at risk for low-dose aspirin discontinuation not related to a safety event.

Whether low-dose aspirin treatment was indicated for primary or secondary CVD prevention had less impact on changes in IR of the non-CVD outcomes and large decreases in the IR of CRC were observed in both settings. The large observed decrease in CRC events changes the benefit-harm profile as compared to when only the benefits for CVD are considered. Treatment decisions regarding low-dose aspirin therapy should therefore take into account all expected benefits and risks as well as patient preferences regarding these outcomes [35].

Direct comparison of IRs across the two age scenarios is hampered due to the average subject in the 50–59 years cohort presenting with more risk factors than the average subject in the 60–69 years cohort. Therefore, these subjects would have a larger risk for CVD events when they reach a similar age as subjects from the 60–69 years cohort.

Reports regarding the treatment duration necessary before a clear effect of low-dose aspirin on colorectal cancer can be observed range from 1 to 5 years, to account for this uncertainty a scenario analysis regarding this parameter was performed [3,22]. When the effect of low-dose aspirin on CRC was assumed to start after three or five years, the IR reduction of non-fatal CRC was smaller than for an effect starting after one year, which is due to the decreased amount of time the treatment can influence the number of events occurring. In contrast, the IR reduction of fatal CRC was larger when the effect was assumed to start after three or five years instead of one year, which is due to the effect-size of low-dose aspirin on fatal CRC used in the model being markedly larger when the low-dose aspirin - CRC effect was assumed to occur after three or five years instead of one year. In the US model, the effect on CRC started after 10 years [33].

The effects of low-dose aspirin treatment tended to decrease with increasing risk of discontinuation, because for subjects who discontinued treatment the probabilities of the outcomes are relatively similar to subjects who did not initiate the treatment. We modeled discontinuation rates more extensively than the US study [33], which allowed us to inspect different discontinuation scenarios. Nevertheless, the trends and effects in both studies are fairly comparable.

4.2. Limitations

The simulation model used to generate the individual patient histories is a useful simplification of the real world. Nevertheless, the model has several limitations.

First, the focus of this model is the effect of low-dose aspirin initiation, therefore it was decided to focus the modelling efforts on low-dose aspirin related aspects of the model instead of perfecting the modelling of potential disease progressions. The main exception here being the CVD events, e.g., it was assumed that previous CVD increased the CVD risk for the rest of the follow-up period.

Second, except for age and presence of a previous CVD, we decided, unlike the US model [33], to keep all other covariates fixed from the start of the follow-up throughout the whole follow-up

period. This was decided since limited information on the temporal evolution of these covariates is available.

Third, information on the risk factors was extracted from the study by Hippisley-Cox *et al.* [13] in which the mean age was lower than in this study, this led to the prevalence of some risk factors, e.g. hypertension and diabetes, being uncharacteristically low. In the model, these risk factors primarily influenced the primary CVD risk which was additionally required to be > 10%, and the CRC risk which was influenced only by body mass index (BMI) and gender. In this model, these risk factors did not influence the risks associated with low-dose aspirin and the uncharacteristically low prevalence might have led to a less favorable benefit-risk profile than what would be observed in practice.

Fourth, the severity of the different non-fatal outcomes is not considered. This would potentially be of interest; however, this would require a large number of additional assumptions, and it was deemed outside the scope of the current model.

Fifth, the output of the model strongly depends on the information selected for informing the model parameters. When information of sufficient quality or relevance was not available or when multiple sources reported significantly different effects a range of options were explored. For example, information regarding the expected discontinuation patterns in our study, which includes primary CVD prevention, was not found. Additionally, it was assumed that subjects who discontinue low-dose aspirin treatment did not resume low-dose aspirin treatment. To mitigate these limitations, a wide range of discontinuation patterns was considered.

Finally, in our model, statins were not included, whereas they were in the US model [33]. It has been argued that the use of statins could reduce aspirin's incremental benefit [36], limiting the use of aspirin for primary prevention to those at high CVD risk (>20%), or those at lower risk who are unable to tolerate statins.

5. Conclusion

The micro-simulation model allowed us to look at the impact of low-dose aspirin in the population of UK subjects indicated for low-dose aspirin use for CVD prevention. Within this population, the decrease in IR and the number of fatal CVD and CRC events was larger than the increase in the IR and the number of fatal safety events, irrespective of whether the low-dose aspirin indication was for primary or secondary CVD prevention.

Acknowledgement

The authors are grateful to Marc Baay (P95 Epidemiology and Pharmacovigilance, Leuven, Belgium), for editorial support.

Author contribution

KB, MSG, PV and JB designed the study. ES collected and all authors discussed the input parameters for the model. JB and KB built the micro-simulation predictive model. All authors provided input to the interpretation of the results. JB and KB wrote the first manuscript draft. All authors critically reviewed the subsequent revisions and approved the final version.

Declaration of conflicting interests

MSG and PV are employees of Bayer AG, the funder of the study. JB, KB and ES are employees of P95 Epidemiology and Pharmacovigilance, which received contracted research fees from Bayer AG for the conduct of the study. LAGR works for the Spanish Centre for Pharmacoepidemiologic Research (Madrid, Spain), which has received research funding from Bayer AG. LAGR also declares honoraria for serving on advisory boards for Bayer AG. AL has served as scientific/medical advisor to Bayer AG. RL has received honorarium from the Aspirin Foundation and is the Chief Investigator of the Add-Aspirin Trial. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This is a Bayer AG initiated and funded study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100851.

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