



# Patient Preferences of Low-Dose Aspirin for Cardiovascular Disease and Colorectal Cancer Prevention in Italy: A Latent Class Analysis

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## Abstract

**Background** Patients taking low-dose aspirin to prevent cardiovascular disease (CVD) may also benefit from a reduced risk of colorectal cancer (CRC).

**Objective** The aim was to examine the preferences of people eligible for preventive treatment with low-dose aspirin and the trade-offs they are willing to make between CVD prevention, CRC prevention, and treatment risks.

**Methods** A cross-sectional study using a discrete choice experiment (DCE) survey was conducted in Italy in 2019 to elicit preferences for three benefit attributes (prevention of ischemic stroke, myocardial infarction, and CRC) and four risk attributes (intracranial and gastrointestinal bleeding, peptic ulcer, and severe allergic reaction) associated with use of low-dose aspirin. Latent class logit models were used to evaluate variation in treatment preferences.

**Results** The DCE survey was completed by 1005 participants eligible for use of low-dose aspirin. A four-class model had the best fit for the primary CVD prevention group ( $n = 491$ ), and a three-class model had the best fit for the secondary CVD prevention group ( $n = 514$ ). For the primary CVD prevention group, where classes differed on age, education level, type 2 diabetes, exercise, and low-dose aspirin use, the most important attributes were intracranial bleeding (two classes), myocardial infarction (one class), and CRC (one class). For the secondary CVD prevention group, where classes differed on various comorbidities, self-reported health, exercise, and CVD medication use, the most important attributes were intracranial bleeding (two classes), myocardial infarction (one class), and gastrointestinal bleeding (one class).

**Conclusion** Patient preferences for the benefits and risks of low-dose aspirin differ significantly among people eligible for treatment as primary or secondary CVD prevention.

## Key Points for Decision Makers

Patient preferences for the benefits and risks of low-dose aspirin differ among people eligible for treatment as primary or secondary cardiovascular disease (CVD) prevention.

The potential colorectal cancer prevention benefit may be especially important to some younger patients eligible for low-dose aspirin for primary prevention of CVD.

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## 1 Introduction

Low-dose aspirin (75–325 mg/day) is one of the most widely used treatments for prevention of cardiovascular (CV) events. Treatment guidelines and recommendations advocate the use of low-dose aspirin for secondary prevention of cardiovascular disease (CVD) and for primary prevention in people at high risk of CV events [1, 2]. An added benefit of low-dose aspirin is protection against colorectal cancer (CRC) [3–5]. A systematic review of the literature and a meta-analysis found that aspirin at any dose may be effective at preventing CRC [5, 6]. A benefit–risk analysis based on the systematic review estimated that for average-risk individuals taking low-dose aspirin prophylactically for 10 years, approximately one third of the overall benefit would be due to the reduction in CRC incidence [6]. Currently, the US Preventive Services Task Force recommends low-dose aspirin for the primary prevention of both CVD and CRC in adults aged 50–59 years who have a 10-year CVD risk  $\geq 20\%$  and in selected adults aged 60–69 years [7].

Low-dose aspirin, however, can be associated with adverse effects, such as gastrointestinal bleeding and, less frequently, intracranial bleeding, gastrointestinal ulcers, and anaphylactic reactions [8–10]. Nonetheless, benefit–risk analyses suggest that low-dose aspirin provides more benefits than risks, especially in individuals who are at high risk of CVD and low risk of gastrointestinal bleeding [1, 11, 12]. The greatest potential benefit in life years and quality-adjusted life years of using low-dose aspirin for primary prevention of CVD and CRC is gained when preventive treatment is initiated earlier (40–69 years of age) by patients and maintained for the remainder of their lives [13].

To be able to recommend appropriate preventative treatment to people at risk of CV events, decision makers need to understand how individuals value aspects such as effectiveness, safety, and convenience [14, 15]. Benefit–risk analyses can provide an objective assessment of the relative benefits and risks of treatments, but they do not provide information on how important different treatment attributes are to patients. Quantitative preference elicitation methods are needed to provide a deeper understanding of patients' preferences and their willingness to make trade-offs between benefits and risks [16]. Previous patient preference studies on primary or secondary prevention of CV events that have used DCE surveys have generally shown that patients highly value reducing the risk of ischaemic stroke, although results have been variable and prevention of CRC has not been included as a potential benefit [17–21].

In the present study, we aimed to understand how people taking or eligible for low-dose aspirin for primary or secondary prevention of CVD value the key CVD prevention benefits and treatment risks, as compared to the CRC prevention benefit; how these preferences vary between individuals; and the contribution of personal characteristics to the variation.

## 2 Methods

### 2.1 Overall Study Design

This was a cross-sectional study conducted in Italy using a discrete choice experiment (DCE) as a stated-preference method. DCEs are based on the idea that the value people place on different options depends on the attributes characterizing them [22, 23], for example, for different treatment options, their levels of efficacy and adverse effects. We applied a mixed-methods approach that combined qualitative patient and physician interviews with a quantitative patient preference elicitation using a DCE, which was conducted following good research practices [24, 25]. Benefit and risk attributes relevant to low-dose aspirin were first identified through a targeted literature review (Online Resource 1, see the electronic supplementary material). We reviewed current practice guidelines of the United States Preventive Services Task Force, European Society of Cardiology, World Health Organization, American College of Chest Physicians, and American Heart Association, as well as published literature, which was identified by searching major medical databases for both qualitative and quantitative preference studies on the use of aspirin, antiplatelet drugs, and non-steroidal anti-inflammatory drugs in primary or secondary prevention of CVD or CRC. The published literature used to identify potential attributes and levels is summarized in Online Resource 1.

The relevance of the identified attributes was explored in qualitative telephone interviews with ten Italian-speaking individuals taking or eligible for low-dose aspirin and three Italian-speaking, medically trained physicians, each with  $\geq 5$  years' experience of prescribing low-dose aspirin for primary and secondary CVD prevention. The aim was to understand why certain benefits and risks of low-dose aspirin are considered important and the willingness to make trade-offs among them. The interviews were conducted using a semi-structured interview guide, and with an emphasis on CVD and CRC prevention. Patients were asked for their perspectives on the benefits and risks of using low-dose aspirin, and physicians were asked about issues and concerns with prescribing low-dose aspirin. In these qualitative interviews, the selected attributes were endorsed to be relevant and no other relevant attributes were found to be missing.

The final attributes and levels were implemented in a DCE survey that was tested with ten Italian-speaking participants taking or eligible for low-dose aspirin for primary or secondary CVD prevention. A semi-structured interview guide was used to determine whether the attributes and levels were understandable to participants; to assess participants' ability to understand the DCE and distinguish between levels; and to confirm that the DCE survey was user friendly. After the first five interviews, changes were made to the wording and organization of the DCE survey. The DCE survey was then tested on participants in a second set of five interviews. Further minor changes were made after the second set of interviews. The final web-based DCE survey was fielded in August to December 2019.

## 2.2 Participants

The study enrolled two groups of participants: adults aged 50–75 years eligible to receive low-dose aspirin (100 mg/day) for primary prevention of CVD and adults aged  $\geq 18$  years eligible to receive low-dose aspirin for secondary prevention of CVD. Eligibility for the primary CVD prevention group was based on a 10-year CVD risk of  $\geq 20\%$  [11]. CVD risk was estimated from self-reported clinical characteristics using the Progetto Cuore risk chart, which assesses the probability of developing a first major CV event based on sex, age, diabetes status, smoking status, systolic blood pressure, and serum total cholesterol level [26]. Eligibility for the secondary CVD prevention group was based on self-reported history of myocardial infarction, ischaemic stroke, transient ischaemic stroke, or angina.

Participants were recruited from two online general population panels with a combined membership of 250,000 in Italy, as well as through physician referrals. Potential participants were contacted by email and screened through a web-based questionnaire. All participants had to be able to read and understand Italian and not be participating in an interventional study. Individuals were ineligible if they belonged to a group for which aspirin use is not recommended (i.e. if they had glucose-6-phosphate dehydrogenase deficiency or another condition for which low-dose aspirin is contraindicated, were being treated with methotrexate, or were pregnant); were employed by a pharmaceutical company; had a direct role in treating patients with CVD; or had a cognitive impairment, hearing difficulty, visual impairment, or acute psychopathology that, in the investigator's or interviewer's judgement, could interfere with the ability to provide online consent and complete an interview or survey. Eligible participants who provided online consent were presented with the objective of the study, a description of the survey structure, and descriptions of the attributes and levels. They then completed the DCE, questions to assess their health literacy

and numeracy using validated scales [27, 28], and questions on demographics and medical history.

## 2.3 DCE

Thirty-six DCE questions were generated using a D-efficient design, which were divided across three blocks with 12 questions each and randomly allocated to participants. Each DCE question presented participants with two hypothetical treatments and a no-treatment option. The three options were defined according to seven attributes: three benefit attributes (decreased risks of ischaemic stroke, myocardial infarction, and CRC) and four risk attributes reflecting potential adverse effects of low-dose aspirin treatment (increased risks of gastrointestinal bleeding, peptic ulcer, intracranial bleeding, and severe allergic reaction) (Table 1), which were introduced to participants before the DCE (Online Resource 2, see the electronic supplementary material). The order of the DCE questions and the order in which individual benefit and risk attributes were presented was randomized among participants, although the benefit attributes were always presented before the risk attributes. An example question is shown in Fig. 1.

In addition to the 12 DCE questions used for capturing participant preferences, two non-experimental questions were included to assess participant attention to the choice questions: a repeated question and a dominance question. The first question was repeated as the seventh question to assess whether participants provided consistent answers. The last question was a dominance question where the no-treatment option had the lowest risk levels for ischemic stroke, myocardial infarction, and CRC and no risk for the adverse effect attributes, and where the risk levels for treatment options A and B were higher for at least one attribute. This question was used to assess whether participants understood and paid attention to the discrete choice task by choosing the no-treatment option.

## 2.4 Statistical Analyses

Statistical analyses were performed using R version 3.6.1 [29], with the packages 'mlogit' [30] and 'gmnl' [31] for analyses of discrete choice data. All participants who fully completed the survey were included in the analyses. Sociodemographic and clinical data were summarized as descriptive statistics.

### 2.4.1 Latent Class Logit Analysis

Latent class logit (LCL) models assume that preferences differ across participants and that participants can be grouped probabilistically according to distinct preference classes, each corresponding to a unique pattern of treatment

**Table 1.** Attributes and levels in the DCE

Attribute <sup>a</sup>	Levels	
	Primary CVD prevention	Secondary CVD prevention
Ischaemic stroke (10-year risk)	5 out of 100	15 out of 100
	10 out of 100	20 out of 100
	15 out of 100 <sup>c</sup>	30 out of 100 <sup>c</sup>
Myocardial infarction (10-year risk)	10 out of 100	40 out of 100
	15 out of 100	50 out of 100
	20 out of 100 <sup>c</sup>	60 out of 100 <sup>c</sup>
Colorectal cancer (10-year risk)	1 out of 100	
	2 out of 100	
	3 out of 100 <sup>c</sup>	
Gastrointestinal bleeding	No risk <sup>b</sup>	
	Increased risk	
Peptic ulcer	No risk <sup>b</sup>	
	Increased risk	
Intracranial bleeding	No risk <sup>b</sup>	
	Increased risk	
Severe allergic reaction	No risk <sup>b</sup>	
	Increased risk	

CVD cardiovascular disease, DCE discrete choice experiment

<sup>a</sup>The following plain language terms were used in the actual survey: stroke (= ischaemic stroke), heart attack (= myocardial infarction), stomach bleeding (= gastrointestinal bleeding), stomach ulcer (= peptic ulcer), and bleeding in the brain (= intracranial bleeding)

<sup>b</sup>This level was selected for the no-treatment option

<sup>c</sup>Indicates a reference level

preferences. In this study, LCL models were fitted separately for the primary and secondary CVD prevention groups. The optimal number of latent classes was determined by fitting LCL models with an increasing number of classes (from 2 to 6) and selecting the one where the Bayesian information criterion was minimized (Online Resource 3, see the electronic supplementary material). Log-likelihood, Akaike information criterion (AIC), AIC3, corrected AIC, and consistent AIC were also calculated.

For each class, maximum likelihood estimates reflecting preferences for marginal changes in the attributes were obtained, together with their standard error, and statistical significance of the estimated preferences was determined by two-sided  $z$ -test at the 5% level. The utility function specified in each model was additive, meaning that the preferences for different attributes were assumed to be independent. The assumption of linearity in preferences for the three benefit attributes (decreased risks of ischaemic stroke, myocardial infarction, and CRC) was tested in linear regression models using multinomial logit model preference estimates and was found to be acceptable, with  $R^2$  in the range 77–100% for the primary CVD prevention group and 97–100% for the secondary CVD prevention group. The benefit attributes

were then entered as continuous variables in the model, which measured the preference for a 1% decrease in risk. The four risk attributes (risks of gastrointestinal bleeding, peptic ulcer, intracranial bleeding, and severe allergic reaction) were entered as binary variables in the model, which measured the preference for a change from “increased risk” to “no risk”. The model also included two constant terms to capture preferences for the no-treatment option and for option A. The latter constant was used to control for potential left–right bias, although as the order of treatment options A and B was not randomized between participants, it may also have captured statistical artefacts of the design.

Model estimates were used to compute relative importance (RI) scores for each attribute in each class. The RI scores, which indicate the value of change across the full range of levels for each individual attribute, were illustrated graphically as radar charts. Confidence intervals for the RI scores were calculated by the Krinsky–Robb procedure [32, 33] using 10,000 draws for the simulation, and Wald tests were used to compare RI profiles across latent classes.

The LCL model estimates were then used to compute the probability of each participant belonging to the different classes and participants were allocated to the class to which

they had the highest probability of belonging. Chi-square test of sample proportions was used to detect significant differences in the personal characteristic compositions of the latent classes. Only characteristics achieving a prevalence of at least 10% observations in each modality were considered. A personal characteristic was identified as a potential predictor of preference heterogeneity when the chi-square test was significant at the 5% level.

### 2.4.2 Data Validity Assessment

Lexicographic preferences were assessed by determining whether participants always chose the treatment option that was better on one of the attributes. Serial non-participation was assessed by determining whether participants always chose treatment option A, treatment option B, or the no-treatment option. Understanding and attention to the DCE task was assessed by determining whether participants selected the dominant no-treatment option in the dominance question. Choice stability was assessed by

determining if participants provided the same answer each time to the repeated question.

## 3 Results

### 3.1 Participants

Of 5134 individuals invited to participate, 2332 completed the screening questionnaire (Fig. 2). The DCE survey was completed by 1005 participants (20% of those invited to participate). Of these, 491 were eligible for or taking low-dose aspirin for primary CVD prevention and 514 were eligible for or taking low-dose aspirin for secondary CVD prevention. In the primary CVD prevention group, the most frequent reasons for study exclusion were having a CV risk < 20% ( $n = 833$ ), unknown systolic blood pressure ( $n = 107$ ), and unknown cholesterol level ( $n = 130$ ). In the secondary CVD prevention group, the most common reason for study exclusion was having disqualifying comorbidities ( $n = 28$ ).

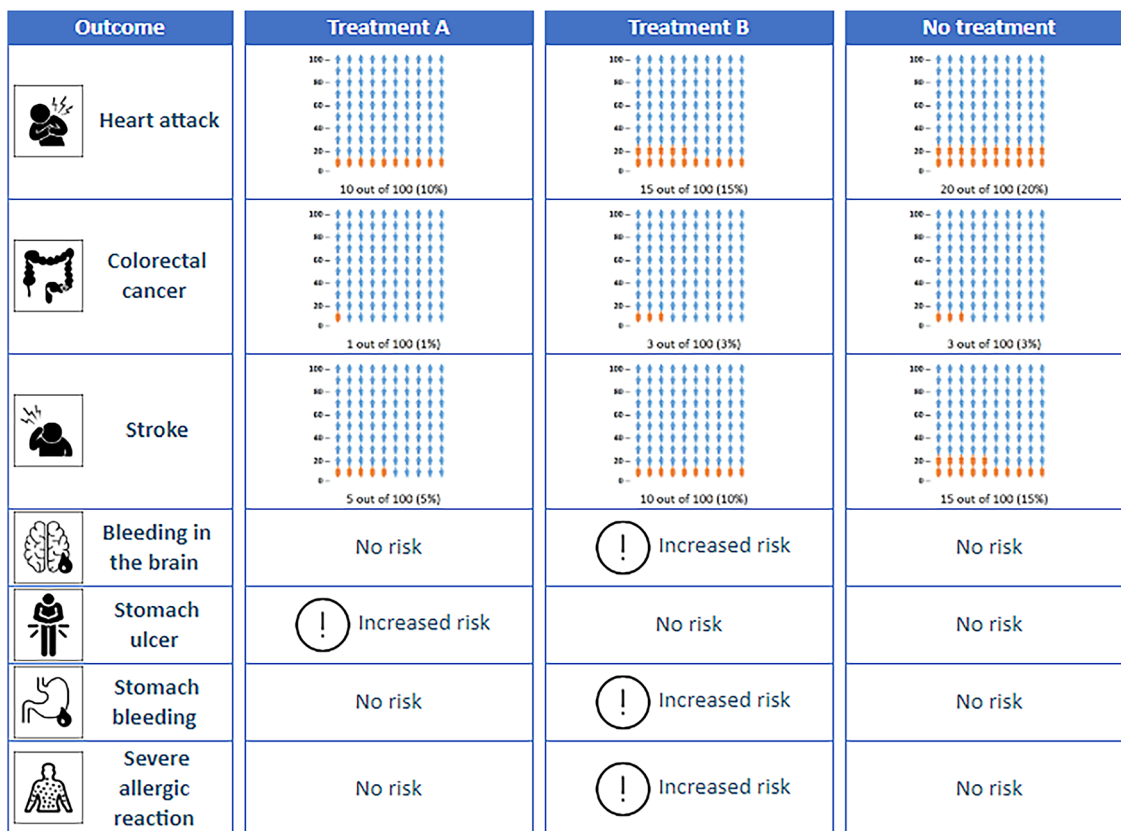


Fig. 1. Example choice question from the survey for primary prevention group. The following plain language terms were used: heart attack (= myocardial infarction), stroke (= ischaemic stroke), bleed-

ing in the brain (= intracranial bleeding), stomach ulcer (= peptic ulcer), and stomach bleeding (= gastrointestinal bleeding)

Fifty-one per cent of participants in the primary CVD prevention group and 48% in the secondary CVD prevention group were female (Table 2). Mean age was 62.5 years for the primary CVD prevention group and 62.2 years for the secondary CVD prevention group. Most participants (72% in the primary CVD prevention group and 75% in the secondary CVD prevention group) were married. Only 24% had at least college education. Mean body mass index was 26.8 kg/m<sup>2</sup> for the primary CVD prevention group and 26.4 kg/m<sup>2</sup> for the secondary CVD prevention group. Fifty-two per cent of participants in the primary CVD prevention group and 58% in the secondary CVD prevention group were current or former smokers.

Frequent comorbidities included type 2 diabetes, reported by 41% of participants in the primary CVD prevention group and 20% of participants in the secondary CVD prevention group. In the secondary CVD prevention group, myocardial infarction was reported by 36% of participants, stable angina by 31%, heart arrhythmias by 29%, transient ischemic attack by 27%, atherosclerosis by 16%, unstable angina by 14%, and ischaemic stroke by 11%. Low-dose aspirin was being taken by 47% of participants in the primary CVD prevention group and 50% of participants in the secondary CVD prevention group.

Based on their answers to the health literacy and numeracy questions, 91% of participants had adequate numeracy but only 35% had adequate health literacy. Ninety-four per cent of participants answered the dominance question correctly, and 66% gave the same answers to the repeated question. Fourteen per cent of participants showed lexicographic preferences (always choosing the treatment option that was better on one of the attributes), most frequently for intracranial bleeding (9%). One percent of participants always chose treatment A or always chose treatment B, and 14% always chose the no-treatment option (Online Resource 4, see the electronic supplementary material).

## 3.2 Participant preferences for treatment attributes

### 3.2.1 Primary CVD Prevention Group

A four-class model (Bayesian information criterion = 8945) best explained the variability in participants' choices for the primary CVD prevention group (Online Resource 5, see the electronic supplementary material). Wald tests indicated that the RI values differed significantly between all classes ( $p = 0.043$  or less; Online Resource 6). Participants in class 1 (37% of participants) had lower education than participants in other classes (21% with higher education vs. 33–37%) (Online Resource 7). The most important treatment attribute for participants in class 1 was intracranial bleeding (RI = 28%) (Fig. 3). For class 2 (26% of participants), a greater proportion of participants were taking low-dose aspirin for

a heart condition than participants in other classes (56% vs. 40–51%). The most important attributes for class 2 were myocardial infarction (RI = 35%) and ischaemic stroke (RI = 29%). Participants in class 3 (19% of participants) exercised less than participants in other classes (38% no exercise/week vs. 27–33%, 24%  $\geq 3$  h exercise/week vs. 32–36%). The most important attributes for class 3 were intracranial bleeding (RI = 32%) and gastrointestinal bleeding (RI = 23%). Lastly, the most important attributes for participants in class 4 (18% of participants), who were younger (27%  $\leq 55$  years vs. 13–16%, 31%  $\geq 65$  years vs. 44–48%) and had less type 2 diabetes (30% vs. 38–48%) than participants in other classes, were CRC (RI = 25%) and intracranial bleeding (RI = 20%).

### 3.2.2 Secondary CVD Prevention Group

For the secondary CVD prevention group, a three-class model (Bayesian information criterion = 7843) best explained the variability in participants' choices (Online Resource 8, see the electronic supplementary material). Wald tests indicated that the RI values differed significantly between all classes ( $p < 0.001$ ; Online Resource 6). Participants in class 1 (37% of participants) were younger than those in other classes (31%  $\leq 55$  years vs. 12–16%, 15%  $\geq 65$  years vs. 57–64%), and more participants in class 1 had inadequate health literacy (87% vs. 60–65%) and a lower level of education (37% primary school vs. 28–33%, 12% higher education vs. 19–25%) (Online Resource 9). There were more current and former smokers in class 1 (9% never smoked vs. 53–67%), and fewer participants in class 1 did  $\geq 3$  h exercise/week (2% vs. 20–32%) compared to other classes. Class 1 also had higher rates of comorbidities (42% congestive heart failure vs. 2–10%, 34% deep vein thrombosis vs. 0–7%, 66% heart arrhythmias vs. 3–15%, 40% heart valve problems vs. 2–8%, 94% hypertension vs. 60–75%, 89% hypercholesterolemia vs. 51–58%, 40% transient ischemic attack vs. 16–23%, 24% unstable angina vs. 9–11%, 31% kidney failure vs. 1%, and 26% type 2 diabetes vs. 15–18%), and hospitalization (83% vs. 13–26%). Fewer participants in class 1 had been taking medications for a heart condition for  $> 5$  years (12% vs. 76–77%), had previously taken anticoagulants or antiplatelets other than aspirin for a heart condition (6% vs. 19–29%), and had a history of myocardial infarction (22% vs. 43–46%) or ischaemic stroke (6% vs. 13–15%). The most important attributes for participants in class 1 were gastrointestinal bleeding (RI = 31%) and intracranial bleeding (RI = 31%) (Fig. 4). Participants in class 2 (35% of participants) had better self-reported health than those in other classes (57% fair/poor health vs. 68%) and more of them reported doing  $\geq 3$  h of exercise per week (32% vs. 2–20%). The most important treatment attribute for participants in class 2 was myocardial infarction (RI = 28%).

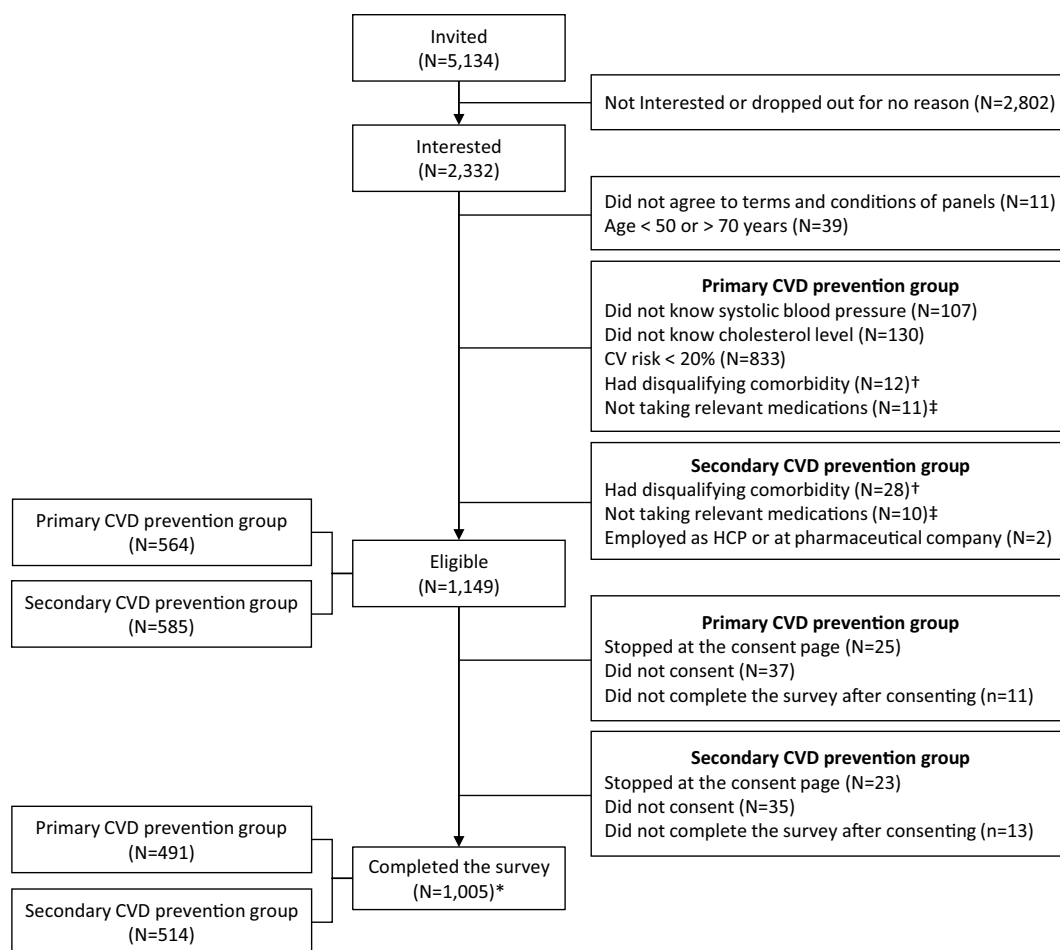
**Table 2.** Demographic and clinical characteristics of participants

Characteristic	Primary CVD prevention ( <i>n</i> = 491)	Secondary CVD prevention ( <i>n</i> = 514)
Sex, <i>n</i> (%)		
Female	248 (51)	247 (48)
Age (years), mean (standard deviation)	62.5 (6.3)	62.2 (6.6)
Marital status, <i>n</i> (%)		
Married	355 (72)	387 (75)
Widowed	36 (7)	45 (9)
Divorced	22 (4)	30 (6)
Separated	30 (6)	25 (5)
Single	48 (10)	27 (5)
Education, <i>n</i> (%)		
Primary school	78 (16)	168 (33)
High school	270 (55)	250 (49)
College or higher	143 (29)	96 (19)
Body mass index (kg/m <sup>2</sup> )		
Mean (standard deviation)	26.8 (5.7)	26.4 (4.3)
Missing, <i>n</i> (%)	19 (4)	76 (15)
Smoking status, <i>n</i> (%)		
Current smoker	222 (45)	144 (28)
Former smoker	32 (7)	156 (30)
Never smoked	237 (48)	214 (42)
Current medical conditions, <i>n</i> (%)		
Atherosclerosis	19 (4)	84 (16)
Cancer other than colorectal cancer	6 (1)	4 (1)
Colorectal cancer	3 (1)	0
Congestive heart failure	8 (2)	98 (19)
Diabetes, type 1	23 (5)	4 (1)
Diabetes, type 2	200 (41)	103 (20)
Heart arrhythmias	17 (3)	151 (29)
Heart valve problems	9 (2)	89 (17)
High cholesterol	465 (95)	344 (67)
Hypertension	464 (95)	394 (77)
Myocardial infarction	0	185 (36)
Peripheral arterial disease	5 (1)	23 (4)
Stable angina	0	159 (31)
Ischaemic stroke	0	58 (11)
Transient ischemic attack	0	137 (27)
Unstable angina	0	71 (14)
Current heart medications, <i>n</i> (%) <sup>a</sup>		
Cholesterol-lowering drugs	420 (86)	367 (71)
Antihypertensive drugs	444 (90)	397 (77)
Low-dose aspirin	230 (47)	258 (50)
Other antiplatelets or anticoagulants Other than aspirin	13 (3)	193 (38)
Other <sup>b</sup>	14 (3)	11 (2)
None	0	0

CVD cardiovascular disease

<sup>a</sup>Information on current heart medications was collected with the question “Which of the following medications are you currently taking for your heart disease?”

<sup>b</sup>Based on participant responses for a free-text “Other” response option



**Fig. 2.** Participant disposition. CV cardiovascular, CVD cardiovascular disease, HCP health care professional. \*A total of 807 (80%) recruited from panels and 198 (20%) recruited from HCP referrals. †Disqualifying comorbidities included glucose-6-phosphate dehydro-

genase deficiency, cognitive impairment, visual impairment, hearing difficulty and acute psychopathology. ‡Relevant medications required to take included cholesterol-lowering drugs, anti-hypertensive drugs, low-dose aspirin and antiplatelets or anticoagulants other than aspirin

And for class 3 (28% of participants), more participants had previously used anticoagulants or antiplatelets other than aspirin compared to other classes (29% vs. 6–19%), although current use of anticoagulants and antiplatelets did not differ between the classes ( $p = 0.459$  for low-dose aspirin,  $p = 0.977$  for other drugs). The most important attribute for class 3 was intracranial bleeding (RI = 28%). CRC prevention was the least important attribute for all secondary CVD prevention classes (RI = 1–8%).

## 4 Discussion

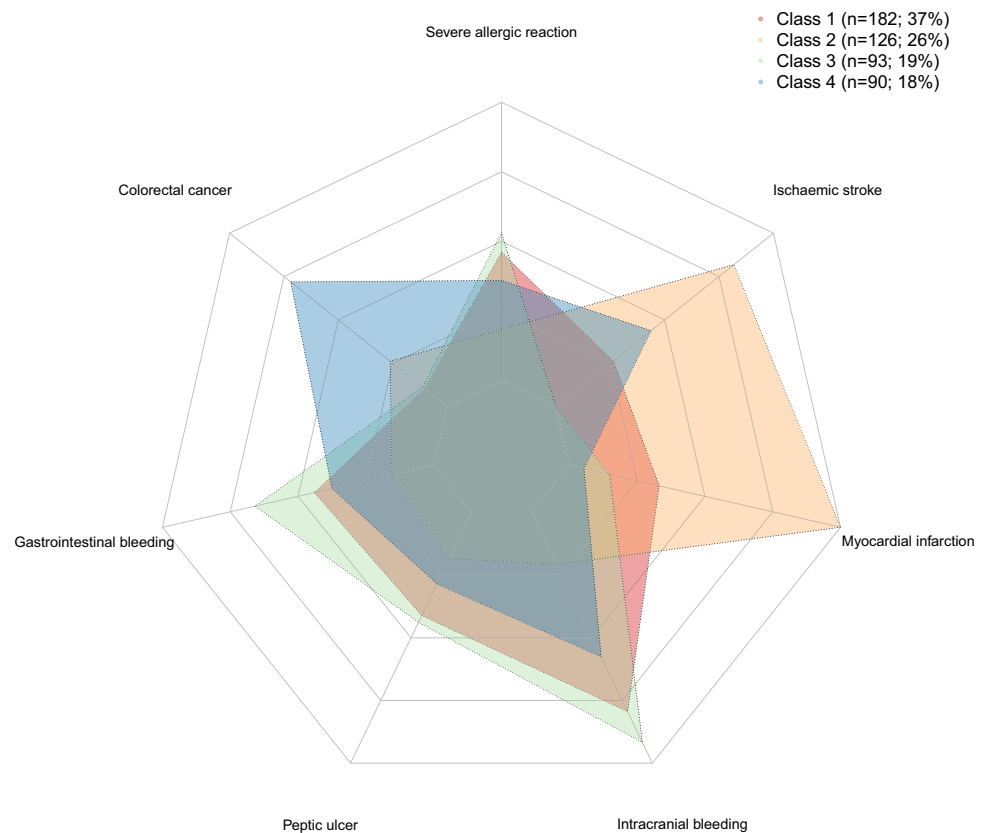
Treatment guidelines recommend low-dose aspirin for secondary prevention of CVD and for primary prevention of CVD in people at high risk of CV events and acceptable risk of bleeding [1, 2], as well as for primary prevention of CRC [7]. Formal benefit–risk analyses suggest that the benefits

of low-dose aspirin outweigh the risks [12, 13]. However, being able to recommend appropriate preventive treatments to people at risk of CV events partly depends on understanding how individuals value treatment attributes. Patients and physicians often value the benefits and risks of prophylactic treatments differently [34–36]. For CVD treatments, patients are less willing than physicians to accept some of the common risks [20].

Patient preference studies have repeatedly found that reducing the risk of CVD (e.g. stroke and myocardial infarction) and avoiding adverse effects of treatment such as bleeding are important treatment considerations for people at risk of CVD [17–19, 21, 37, 38]. The frequency and costs of treatment are also important to patients [39]. The current study, conducted in Italy, where low-dose aspirin (100 mg/day) is recommended for primary and secondary CVD prevention, found that preferences towards the treatment benefits and potential adverse effects of low-dose



**Fig. 3.** Relative importance by preference class for the primary cardiovascular disease prevention group.



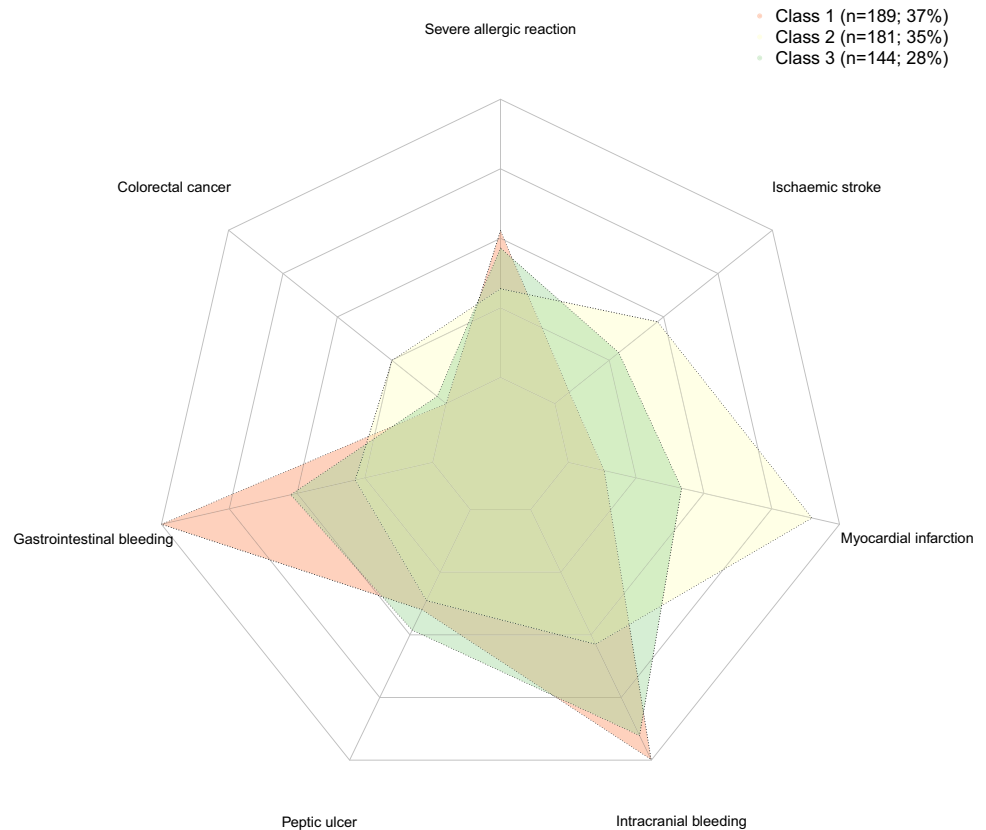
aspirin varied significantly both between and within the primary and secondary CVD prevention study groups. Nevertheless, seven discrete classes of preferences could be distinguished. Preventing myocardial infarction and ischaemic stroke were the most important treatment attributes for a class of participants in the primary CVD prevention group whose rate of current low-dose aspirin use was higher compared to other classes, possibly because they were aware of being at particularly high risk for these events. We also found that avoiding intracranial and gastrointestinal bleeding were most important treatment attributes to a class of participants in the secondary CVD prevention group with higher rates of several comorbidities and of hospitalization, indicating that they were less concerned about benefits than risks even though many of them had already experienced angina or a CV event. This could be due to the participants being concerned about the burden of further hospitalizations or additional comorbidities. Avoiding an increased risk of intracranial bleeding was the most important treatment attribute to another class of participants in the secondary CVD prevention group.

An added probable benefit of low-dose aspirin, not included in previous DCE low-dose aspirin studies, is protection against CRC [3–5]. A previous non-DCE study found that the CRC prevention benefit increased the acceptability of aspirin [40]. We found that the additional CRC prevention

benefit was more important for patients in the primary CVD prevention group than in the secondary CVD prevention group. Moreover, one class of participants in the primary CVD prevention group, who tended to be younger, considered CRC prevention the most important treatment attribute.

The LCL models used in this study provide important information about the preferences of individuals taking low-dose aspirin for primary or secondary prevention of CVD; however, LCL models have some limitations [41]. First, as with all limited dependent variable models, the preference estimates are confounded with the utility scale, such that two classes may represent the same preferences but with different scales. However, we did not detect major scaling issues and we computed RI, which is a scale-free measure of preferences. Second, while the information obtained with LCL models provides insight into the preferences of different groups of patients at the population level, it cannot be used to guide treatment selection for individual patients. Another limitation of this study is that it relied on self-reporting of medical history and current and past treatments by participants. Any inaccuracies in the information provided by participants may have resulted in errors in assigning them to the primary and secondary CVD prevention groups and in the analyses of treatment preferences according to clinical characteristics. However, such errors would be unlikely to affect the finding that all latent classes considered the

**Fig. 4.** Relative importance by preference class for the secondary cardiovascular disease prevention group



potential for adverse effects important. A further potential limitation is that differences in the strength of evidence for the potential benefits and risks of low-dose aspirin treatment (with evidence for prevention of myocardial infarction being stronger than that for CRC prevention, for example) were not explained to participants. Also, the adverse effect attribute levels were simply “increased risk” and “no risk”, with no explicit consideration of changes across the probability scale. Moreover, some participants may not have given the survey questions adequate consideration. We reduced the potential impact of this by including a number of irrelevant options for some screening questions and screening out people who did not carefully consider all the listed options, for example, by indicating that they were taking an antidepressant for their heart diseases. Also, 94% of participants answered the dominance question correctly, a rate similar to other DCEs in the health domain [42]. This suggests that the participants paid sufficient attention to the survey. The overall participation rate of 20% (1005/5134) may have induced selection bias, but it is higher than for other patient preference studies with panel recruitment [18, 43]. Furthermore, only a third of the study participants had adequate health literacy, which may have limited their understanding of the study materials. However, similarly low levels of health literacy were observed in another study in Italy [44], and no major issues with the final survey were detected in cognitive

pilot interviews. Finally, this study was performed in a single country with only a quarter of the participants having a college education. Moreover, the primary CVD prevention study group was considerably younger than the general Italian population using low-dose aspirin for primary prevention of CVD [45], partially because people older than 75 years were excluded. Our results may therefore not be generalizable to other countries or populations.

## 5 Conclusion

Adherence to low-dose aspirin regimes is suboptimal, and patient education is imperative for achieving improvements in adherence [46]. Understanding how treatment preferences vary between individuals can help health care professionals to better communicate information on those benefits and risks of low-risk aspirin that matter most to a particular patient. This study indicated that the potential CRC prevention benefit may be especially important to some younger patients eligible for low-dose aspirin for primary prevention of CVD, and that many patients eligible for low-dose aspirin for primary or secondary CVD prevention are likely to be concerned by potential adverse effects of treatment. Translation of these insights to decision making in the clinic has the

potential to improve patient education, which may ultimately lead to better treatment outcomes.

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## Declarations

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**Conflict of interest** Pareen Vora, Montse Soriano Gabarró, and Ulrike Wissinger are employees of Bayer. Tommi Tervonen, Jaemin Seo, Nicolas Krucien, and Kevin Marsh are employees of Evidera, which received funding from Bayer to conduct the research. Raffaele De Caterina has received fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, AstraZeneca, Sanofi-Aventis, Eli Lilly, and Novartis; and grant support from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, and AstraZeneca.

**Ethics approval** Ethical approval for the study was granted by Ethical & Independent Review Services institutional review board (Independence, MO, USA) before any study procedures were initiated (institutional review board reference number 18118-01 for initial submission, 18118-02 for continuing review, and 18118-02A for additional recruitment templates for main data collection).

**Consent** All individual participants included in the study provided online consent to participate.

**Availability of data and material** The datasets generated during and/or analysed during the current study are not publicly available as no consent was sought from participants to allow sharing of data with third parties.

**Code availability** Not applicable.

**Author contributions** TT contributed to the conception, design, and implementation of the work and analysis, interpretation of data for the work, and drafting and revision of the manuscript. PV contributed to the conception, design, and implementation of the work, interpretation of data for the work, and revision of the manuscript. JS contributed to the design and implementation of the work, acquisition and interpretation of data for the work, and drafting and revision of the manuscript. NK contributed to analysis, interpretation of data for the work, and revision of the manuscript. KM contributed to the design and implementation of the work, and revision of the manuscript. RDC contributed to interpretation of data for the work and revision of the manuscript. UW contributed to design of the work, and revision of the manuscript. MSG contributed to the conception, design and implementation of the work, interpretation of data for the work, and revision of the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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