

# Effect of aspirin on the diagnostic accuracy of the faecal immunochemical test for colorectal advanced neoplasia

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## Abstract

**Background:** Aspirin (ASA) is a drug that can cause gastrointestinal lesions and symptoms. Colorectal cancer (CRC) is the most prevalent type of cancer in Western countries. We assessed the effect of aspirin on the diagnostic accuracy of the faecal immunochemical test (FIT) for CRC and/or advanced neoplasia (AN) in patients undergoing colonoscopy for gastrointestinal symptoms.

**Methods:** We conducted a prospective multicentre observational study of diagnostic tests that included patients with gastrointestinal symptoms undergoing colonoscopy between March 2012 and 2014 (the COLONPREDICT study). Symptoms were assessed and a FIT and blood tests assessing haemoglobin and carcinoembryonic antigen (CEA) levels were performed.

**Results:** The study included 3052 patients: A total of 2567 did not take aspirin (non-user group) and 485 (16%) took aspirin (user group). Continuous treatment with ASA did not change the AUC (0.88, 0.82;  $p = 0.06$ ), sensitivity (92%, 88%;  $p = 0.5$ ) or specificity (71%, 67%;  $p = 0.2$ ) of the FIT for CRC detection. Similarly, we found no differences in the AUC (0.81, 0.79;  $p = 0.6$ ), sensitivity (74%, 75.5%;  $p = 0.3$ ) or specificity (76%, 73.6%;  $p = 0.3$ ) for AN detection. Patients with an aspirin use of  $\geq 300$  mg/day had a lower prevalence of AN and the sensitivity, specificity and AUC for AN for these patients were 54%, 68% and 0.66, significantly lower than for the non-user group ( $p = 0.03$ ).

**Conclusions:** Aspirin does not modify the diagnostic accuracy of FIT for CRC and/or AN in patients with gastrointestinal symptoms. Aspirin use of  $\geq 300$  mg/day decreases the accuracy of the test.

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## Introduction

Colorectal cancer (CRC) is the most prevalent type of cancer in Western countries, and screening for this type of cancer has led to a decrease in its incidence and associated mortality.<sup>1,2</sup> The two most widely accepted techniques for screening in most countries are colonoscopy and the faecal immunochemical test (FIT).<sup>1,3</sup> Most CRC diagnoses are made in people who seek medical attention for symptoms that include rectal bleeding, change in intestinal rhythm, abdominal pain and anaemia. These symptoms are very common in the general population, hence, various risk factors have been used to identify individuals who are more likely to have CRC. Recently, published studies have suggested that FIT is the approach with greatest diagnostic accuracy for CRC detection in symptomatic patients<sup>4,5</sup> as a sole biomarker or within prediction models.

Studies conducted by our research group have found that the combination of certain signs and symptoms, older age, male sex and a positive FIT result are associated with a 10× higher risk of CRC.<sup>4,5</sup> In patients who meet these criteria, colonoscopy must be performed. It has been speculated that FIT results may be modified by certain drugs such as aspirin. Neither antiplatelet drugs nor oral anticoagulants affect the predictive value of the test in asymptomatic populations taking part in screening programmes; however, we do not know the potential effect of aspirin use on FIT in people with gastrointestinal symptoms.<sup>6,7</sup> Aspirin has been shown to, on the one hand, decrease the risk of colon polyps<sup>8</sup> and on the other, increase the likelihood of gastrointestinal complaints and anaemia.<sup>9</sup>

Our objective was to assess whether aspirin use changes the diagnostic accuracy of FIT in patients with gastrointestinal symptoms.

## Patients and methods

### Design

We carried out a post-hoc analysis to assess whether aspirin use affects the diagnostic accuracy of FIT in the derivation and validation cohorts from the COLONPREDICT study.<sup>4,5</sup> COLONPREDICT was a blind, multicentre cross-sectional study of diagnostic tests. The study sought to create and validate a CRC-predictive index based on available biomarkers and clinical and demographic data.

### Population

The study population consisted of consecutive patients with gastrointestinal symptoms referred for colonoscopy from primary and secondary care. Patients were excluded if they were younger than 18 years, pregnant, or asymptomatic and undergoing colonoscopy for CRC screening, had a history of colonic disease and were undergoing surveillance colonoscopy, required hospital admission, or had symptoms that had ceased within three months before evaluation. The trial protocol was approved by the Clinical Research Ethics Committee of Galicia (Code 2011/038). Patients provided written informed consent before inclusion.

### Laboratory testing

Patients were administered by nurses specifically trained in the assessment of gastrointestinal symptoms or doctors a questionnaire that included questions related to medication use. In addition, all patients underwent a blood test that included measurement of haemoglobin and carcinoembryonic antigen (CEA) levels, a FIT and colonoscopy.

All individuals collected a stool sample the week before colonoscopy from one bowel movement without specific diet or medication restrictions. They were specifically instructed to sample a stool with no visible blood. FIT was performed using the automated OCsensor™ (Eiken Chemical Co, Tokyo, Japan). Samples were processed as previously described<sup>4</sup> at each regional reference hospital. Patients with  $\geq 20$  µg of haemoglobin per gram of faeces were classified as positive. Moreover, we measured serum haemoglobin levels and mean corpuscular volume with a Beckman Coulter Autoanalyzer (Beckman Coulter Inc, CA, USA) and serum CEA levels using a chemiluminescent microparticle immunoassay (UniCel DXI 800; Beckman Coulter, CA, USA).

### Definition of cohorts

Patients were divided into two groups: users and non-users. We defined the 'users' as those reporting chronic use of aspirin. Chronic use was defined as patients taking aspirin for more than one year at least five days a week. 'Non-users' were individuals who did not report chronic use of aspirin. Patients who reported a sporadic intake of aspirin were excluded. The dose

and duration of aspirin use were verified during the patient's interview with the physician or nurse when the medical history was reviewed. At some participating centres, dosage and duration of aspirin use were also verified by inspecting their electronic prescription records and the number of pack of pills withdrawn from the pharmacy. It was recommended that patients not suspend aspirin use before FIT or prior to colonoscopy.

### Colonoscopy

All colonoscopies were performed by experienced endoscopists (each performing >200 colonoscopies per year). Colonoscopy was performed blind to the questionnaire and other test results. Before colonoscopy, endoscopists performed a digital rectal examination and an anoscopy. Colonoscopy quality was ensured by following the Spanish Gastroenterological Association and Spanish Society for Digestive Endoscopy guidelines.<sup>10</sup> We considered colonoscopy complete if cecal intubation is achieved or a complete neoplastic stenosis is found.

### Outcomes

The main outcome was the diagnosis of CRC and advanced neoplasia (AN). Adenomas  $\geq 10$  mm in size, with villous architecture, high-grade dysplasia or intramucosal carcinoma were classified as advanced adenomas. The location of the CRC was described as rectum, or distal or proximal to the splenic flexure. Tumour staging was performed according to the seventh edition of the American Joint Committee on Cancer (AJCC) classification.<sup>11</sup> AN was defined as advanced adenoma or invasive cancer. Data from each individual were recorded in an online database.

### Statistical analysis

A descriptive analysis of the sample was performed. Comparisons between the groups (non-users and users) were conducted using chi-square and/or Fisher's exact tests for categorical variables, and the non-parametric Mann-Whitney test for continuous variables.

Patients were classified into three groups by level of aspirin use: none, less than 300 mg/day and 300 mg/day or more. The effect of aspirin use on the positivity of the FIT was analysed with logistic regression, calculating odds ratios (both crude and adjusted for covariates reflecting other factors potentially involved). To assess the accuracy of the FIT in the diagnosis of CRC and AN, sensitivity, specificity and areas under the receiver operating characteristic curve (AUCs) were calculated, together with their confidence intervals. These

estimators were compared between groups of aspirin use with a chi-square test to compare proportions and homogeneity of the areas.

All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 and MedCalc, version 12.7.0.0.

## Results

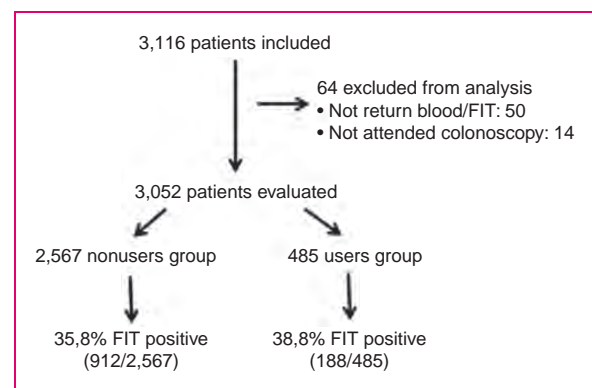
### Description of the sample

We included 3116 patients, of whom 64 were subsequently excluded, yielding a final sample of 3052 (Figure 1). Of the 3052 participants, 2567 (84%) reported not taking aspirin (non-user group), and 485 (16%) taking aspirin (user group). In the user group, 427 (88%) took less than 300 mg/day of aspirin while 58 individuals took more  $\geq 300$  mg/day. As expected, more men were taking aspirin than women ( $p < 0.05$ ) and users were older than non-users ( $p < 0.001$ ) (Table 1).

We detected CRC in 350 (11.4%) patients, located in the rectum, in the distal and proximal colon respectively in 28.4%, 50.7% and 20.9% of cases. The tumour staging was: 0 in 2.8% of cases, I in 18.6%, II in 25.1%, III in 37.7% and IV in 15.8%. Additionally, we found advanced adenomas in 739 (24.2%) patients. Overall, we detected AN in 1089 (35.6%) patients.

### Effect of aspirin use on FIT results

The FIT was positive in 36% of patients overall (1100/3052), 38.8% (188/485) in the user group and 35.5% (912/2567) in the non-user group ( $p = 0.2$ ). Patients with positive results had a higher mean age than those with negative results (67.7 vs 63.7 years;  $p < 0.0005$ ). The FIT was positive in 23.1% (99/428) of patients under 50 years and 37.9% (996/2624) of



**Figure 1.** Recruitment and participant flow through the study. FIT: faecal immunochemical test.

**Table 1.** Characteristics of individuals included in the study.

	Total (n = 3052)	User group (n = 485)	Non-user group (n = 2567)	p value <sup>a</sup>
Positive FIT result	1090 (35.7%)	188 (38.8%)	912 (35.8%)	0.2
Age (years)	67 (SD: 13)	72.5 (SD: 9)	63.7(SD: 14)	<0.0005
Male sex (%)	1528 (50%)	282 (58.1%)	1246 (48.5%)	<0.0005
Serum haemoglobin (mean, SD g/dl)	13.3 (2.6)	12.9 (1.9)	13.4 (2.8)	<0.0005
<10 g/dl		38 (7.8%)	135 (5.2%)	
10–12 g/dl		105 (21.6%)	403 (15.6%)	<0.0005
>12 g/dl		342 (70.6%)	2029 (79%)	
Carcinoembryonic antigen (mg/dl)	1.8 (1–3.1)	2 (1.3–3.1)	1.7 (1–2.8)	<0.001
<3 mg/dl		350 (72.2%)	2014 (78.9%)	0.01
≥3 mg/dl		135 (27.8%)	542 (21.1%)	
Results of colonoscopy				
Cancer	350 (11.4%)	51 (10.5%)	299 (11.6%)	0.5
Advanced adenoma	739 (24.2%)	123 (25.3%)	616 (23.9%)	

<sup>a</sup>p value Mann-Whitney U. FIT: faecal immunochemical test.

those aged 50 years and above ( $p < 0.0005$ ). Further, those who had positive results tended to have a lower haemoglobin concentration than those with negative results (13.2 vs 13.4 g/dl,  $p = 0.06$ ). The test was positive in 38.9% (661/1699) patients with haematochezia and only 32.3% (438/1353) of those who didn't show this sign ( $p < 0.0005$ ). In the multivariate analysis (Table 2), we found that men, individuals above 50 years of age, with a low concentration of haemoglobin, haematochezia or levels of CEA above 3 mg/dl were more likely to have a positive FIT result.

### Diagnostic accuracy for CRC in users and non-users

In the user group, there were 51 cases (10.5%) of CRC, of whom 44 (88%) had a positive FIT result. The sensitivity and specificity of the FIT for CRC in the user group were 88% and 67%, respectively, while the AUC was 0.82 (Figure 2). In this group, 123 (25.3%) individuals were found to have advanced adenoma, 82 (67%) of the cases being detected with the FIT. The sensitivity and specificity of the FIT for AN, in the user group were 75% and 73%, respectively (Table 3), while the AUC was 0.79 (Figure 3).

In the non-user group, there were 299 (11.6%) cases of CRC, of whom 275 (92%) had a positive FIT result. The sensitivity and specificity of the FIT for CRC in the non-user group were 92% and 71%, respectively, and the AUC was 0.88 (Table 3). In this group, we detected 616 (23.9%) cases of advanced adenoma, of which 351 (56%) cases were detected with the FIT. The sensitivity and specificity of the FIT for AN in the user group were

74% and 76%, respectively, while the AUC was 0.81. We did not observe significant differences between the user and non-user groups in terms of sensitivity, specificity and AUCs for AN.

### Effect of aspirin dose on diagnostic accuracy

When we assessed whether the aspirin dose (more or less than 300 mg/day) modified the presence of AN, we found a lower risk of developing AN and CRC among those who took a dose  $\geq 300$  mg/day (Table 4). Among the 427 patients who took less than 300 mg/day, 50 (11.7%) were found to have CRC, while we found just one (1.7%) patient with CRC among those who took 300 mg/day or more. The mean duration of aspirin use was higher in patients taking  $\geq 300$  mg/day than those using lower doses (less than 300 mg/day) (56 vs 43 months,  $p < 0.05$ ). We did not observe significant differences in FIT positivity as a function of aspirin dose: 38.8% among those taking doses  $\geq 300$  mg/day vs 37.9% among those taking less than 300 mg/day. For AN, the sensitivity and specificity of the FIT in the group taking  $\geq 300$  mg/day were 54% and 68% compared to 77% and 74% in those taking less (under 300 mg/day), the differences not being significant (Table 5), while the AUC was 0.79 among those taking  $< 300$  mg/day and 0.66 among those using higher doses ( $\geq 300$  mg/day) ( $p = 0.09$ ).

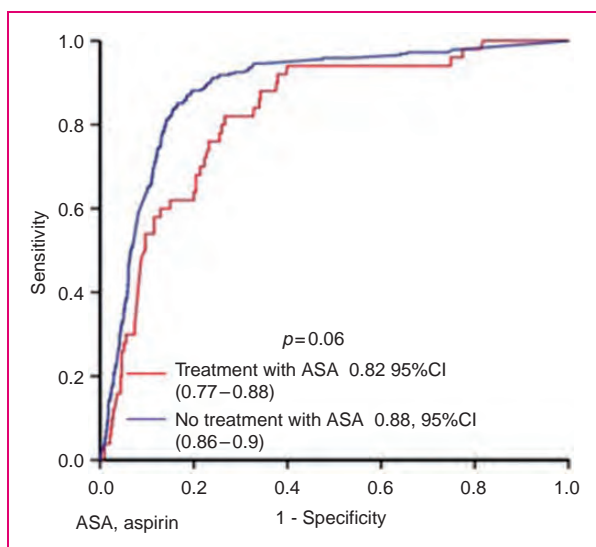
### Discussion

In this study, we have observed no significant difference in the rate of positive FIT results in patients seeking

**Table 2.** Factors associated with a diagnosis of advanced neoplasia in patients with a positive faecal immunochemical test result.

	Univariate analysis				Multivariate analysis	
	N	+ FIT	OR (95% CI)	p value	OR (95% CI)	p value
<b>Sex</b>						
Female	1524	481 (31.5)	Reference			
Male	1528	619 (40.5)	1.5 (1.3-1.7)	<0.0005	1.5 (1.3-1.8)	<0.0005
<b>Aged (years)</b>						
< 50	428	99 (23.1)	Reference			
≥ 50	2624	1001 (38.1)	2.0 (1.5-2.5)	<0.0005	2.0 (1.5-2.6)	<0.0005
<b>Aspirin</b>						
Not	2567	912 (35.5)	Reference		Reference	
Yes	485	188 (38.8)	1.1 (0.9-1.4)	0.2	0.9 (0.7-1.2)	0.3
< 300 mg	427	167 (38.8)	1.1 (0.9-1.4)	0.2	1.0 (0.8-1.3)	1.0
≥300 mg	58	22 (37.9)	1.0 (0.6-1.7)	0.9	0.5 (0.3-1.1)	0.08
<b>Haematochezia</b>						
Not	1353	438 (32.3)	Reference		Reference	
Yes	1699	661 (38.9)	1.3 (1.1-1.5)	<0.0005	1.5 (1.3-1.8)	<0.0005
<b>Haemoglobin</b>						
> 12 g/dl	2371	790 (33.3)	Reference		Reference	
10-12 g/dl	508	224 (44)	1.5 (1.2-1.9)	<0.0005	1.7 (1.4-2.2)	0.0005
<10 g/dl	173	86 (49.7)	1.9 (1.4-2.7)	<0.0005	1.9 (1.3-2.8)	0.0005
<b>Carcinoembryonic antigen</b>						
< 3 mg /dl	2364	765 (32.3)	Reference		Reference	
≥ 3 mg/dl	677	334 (48.6)	1.9 (1.6-2.3)	<0.0005	1.6 (1.3-2.0)	<0.0005

FIT: faecal immunochemical test; OR: odds ratio; CI: confidence interval.



**Figure 2.** Receiver operating characteristic curve analysis for colorectal cancer diagnosis with faecal immunochemical test as a function of aspirin use. ASA: acetylsalicylic acid; CI: confidence interval.

**Table 3.** Sensitivity, specificity and area under the receiver operating characteristic curve (AUC) for colorectal cancer and advanced neoplasia as a function of aspirin use.

	Advanced neoplasia		Significance <sup>a</sup>
	Non-users	Users	
Sensitivity <sup>b</sup>	74 (70-77)	75 (66-82)	0.9
Specificity <sup>b</sup>	76 (74-78)	73 (68-78)	0.28
AUC <sup>2</sup>	0.81 (0.78-0.82)	0.79 (0.74-0.83)	0.6
<b>Colorectal cancer</b>			
	non-users	Users	Significance <sup>a</sup>
Sensitivity <sup>b</sup>	92 (88-95)	88.00 (75-95)	0.5
Specificity <sup>b</sup>	71 (69-73)	66.97 (62-71)	0.19
AUC <sup>b</sup>	0.88 (0.86-0.90)	0.82 (0.77-0.88)	0.06

<sup>a</sup>Differences with p < 0.05 are considered statistically significant.

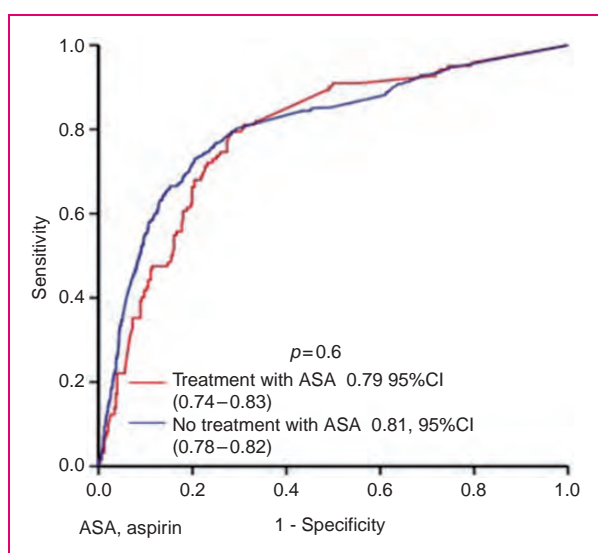
<sup>b</sup>Values are expressed as percentage and 95% confidence interval.

medical attention for digestive symptoms as a function of whether they reported aspirin use. The sensitivity of the FIT was similar in the two groups (75% users vs 74% non-users).

Levi et al.<sup>12</sup> in a retrospective study with fewer aspirin users (980 non-users and 170 users) also found no differences in sensitivity or specificity of the FIT in symptomatic patients. In that study, the sensitivity, specificity and positive predictive value (PPV) of the FIT for AN in aspirin users were 66%, 92% and 52%, respectively, while these values were 46%, 93% and 38%, respectively, in the control group. Our findings differ from these results in that we found sensitivity, specificity and PPV in the non-user group of 74, 76% and 50%, respectively. Levi et al. do not provide information about the positivity of the test. The differences

observed in the test sensitivity may be due to the differences in prevalence of the lesions detected and the design of the study (retrospective vs prospective). In contrast to our study, the prevalence of AN in the study by Levi et al.<sup>12</sup> was very low (9.3%), comparable to values of 1.3% to 10.7% found in asymptomatic individuals in prospective studies.<sup>13,14</sup> Research based on asymptomatic individuals, such as the COLONPREV study,<sup>14</sup> has also failed to find differences in the predictive value of the test between aspirin users and non-users. Analysing the predictive value as a function of aspirin use, we found that the predictive value of the FIT was lower for those taking the highest doses of the drug. Further, the prevalence of AN was lower in patients on higher doses of aspirin (>300 mg/day). It is known that aspirin reduces the occurrence of adenomas<sup>8,15</sup> and that a lower prevalence of lesions decreases the predictive value of diagnostic tests. With regards to the most suitable dose of aspirin to reduce the occurrence of adenomas, there is no consensus between studies<sup>15,16</sup> and this may be due to the number of patients included, the type of patients (moderate vs high risk) or the duration of aspirin use.

The prevalence of AN in our study was high (35.6%). Blumenstein et al.<sup>17</sup> observed in a prospective study that the prevalence of CRC in individuals of at least 55 years of age was equivalent in symptomatic individuals (1.21%) and the control group (1.02%); advanced adenomas were observed in significantly fewer symptomatic patients (5.67%) than matched asymptomatic controls (8.03%); and finally, polyps were found significantly less often in symptomatic patients (25.0%) than in matched controls (33.6%). However, in another study,<sup>18</sup> the prevalence was somewhat higher, with colonic neoplasia and CRC being identified in 17.3% and 11.3% cases, respectively of a total 1013 symptomatic individuals (mean age 59.9 years, 52.3% females) from a multi-ethnic Asian background. The high prevalence we found could be attributable to the inclusion of patients referred for in-hospital high-resolution consultation for colon cancer.



**Figure 3.** Receiver operating characteristic curve analysis for advanced neoplasia diagnosis with faecal immunochemical test as a function of aspirin use.

ASA: acetylsalicylic acid; CI: confidence interval.

**Table 4.** Prevalence of advanced adenoma and cancer as a function of aspirin dose.

	Individuals	AA no. (%)	<i>p</i> value	CRC No. (%)	<i>p</i> value
Non-user group	2567	616 (24%)		299 (11.6%)	
User group					
Aspirin < 300 mg per day	427	111 (25.9%)	0.9	50 (11.7%)	0.07
Aspirin ≥ 300 mg per day	58	12 (20.6%)		1 (1.7%)	

AA: advanced adenoma; CRC: colorectal cancer

**Table 5.** Sensitivity, specificity and area under the receiver-operating characteristic curve (AUC) for advanced neoplasia as a function of aspirin dose.

	Advanced neoplasia		Significance <sup>a</sup>
	ASA < 300 mg	ASA ≥ 300 mg	
Sensitivity <sup>b</sup>	77 (67–84)	54 (23–83)	0.19
Specificity <sup>b</sup>	74 (68–78)	68 (52–80)	0.49
ROC curve <sup>b</sup>	0.79 (0.75–0.85)	0.66 (0.50–0.82)	0.09

<sup>a</sup>Differences with  $p < 0.05$  are considered statistically significant.

<sup>b</sup>Values are expressed as percentage and 95% confidence interval.

ASA: acetylsalicylic acid; ROC: receiver operating characteristic.

The prevalence of aspirin use in the general population is very high. Low-dose aspirin use is indicated for primary prevention of cardiovascular events. Aspirin is taken by about 17% of asymptomatic individuals aged over 65 years<sup>19</sup> and 25% of patients admitted to hospital for gastrointestinal bleeding. This drug is known to cause lesions in the stomach and duodenum, and can lead to an increase in the bleeding of colon lesions.<sup>20</sup> In our study, 16% of symptomatic patients took aspirin. Aspirin use among asymptomatic people who attended screening tests ranged between 8.9% and 12% with a mean age between 59 and 62 years of age, respectively.<sup>6,13</sup> As in previous studies, we found that aspirin users were older and more likely to be male.<sup>13</sup>

Further, aspirin may increase the onset of digestive symptoms that can lead patients to seek medical attention. A meta-analysis of 59 studies found that 5.2% of individuals receiving aspirin reported a minor gastrointestinal complaint (abdominal pain, dyspepsia, or nausea/vomiting), vs 3.7% of placebo participants. The corresponding summary odds ratio was 1.46, while the odds ratios for dyspepsia and abdominal pain were 3.17 and 1.92, respectively.<sup>9</sup> Further, aspirin enhances the onset of anaemia and gastrointestinal bleeding.<sup>21</sup> In our study, we found that aspirin users had lower levels of haemoglobin, and this may be related to the harmful effect of this drug on the gastrointestinal mucosa, since the prevalence of AN was similar in both groups. Despite the potential adverse effects of aspirin, treatment cessation may increase the likelihood of cardiovascular complications (primarily, cerebral stroke and ischaemic heart disease).

The present study is strengthened by a number of observations. First, it is a post-hoc analysis within a prospective clinical trial in symptomatic patients without selection bias, which should minimise confounders for the detection of advanced adenomas and AN. Second, the number of cases analysed is higher than that reported to date with a high prevalence of CRC. Third, this is the largest study that assesses the effect of

a treatment with aspirin in terms of diagnostic accuracy for CRC and AN.

The study also has some limitations. First, we do not know to what extent patients who were taking aspirin may show a positive FIT result due to lesions in the stomach and small intestine. Additionally, we were not able to determine whether the clinical signs that prompted patients to seek medical attention were related to aspirin intake.

In summary, aspirin use did not change the diagnostic accuracy of FIT in patients with gastrointestinal symptoms. For this reason, we do not recommend discontinuation of aspirin treatment in patients who seek medical attention for symptoms suggestive of CRC.

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The authors' contributions were as follows: LB, JC, PV and MS participated in the study design; JC, EQ, MS, VAS, FFB, MA, JB, RC, AG, AF, LT, DR, MD, VH, and LB in the collection, analysis, and interpretation of data; JC, CS and LB in the writing of the report; and all the authors decided to submit the article for publication. All authors had full access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

### Declaration of conflicting interests

None declared.

### Ethics approval

The study was approved by the Clinical Research Ethics Committee of Galicia (Code 2011/038).

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### Informed consent

Patients provided written informed consent.

### Supplementary note

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