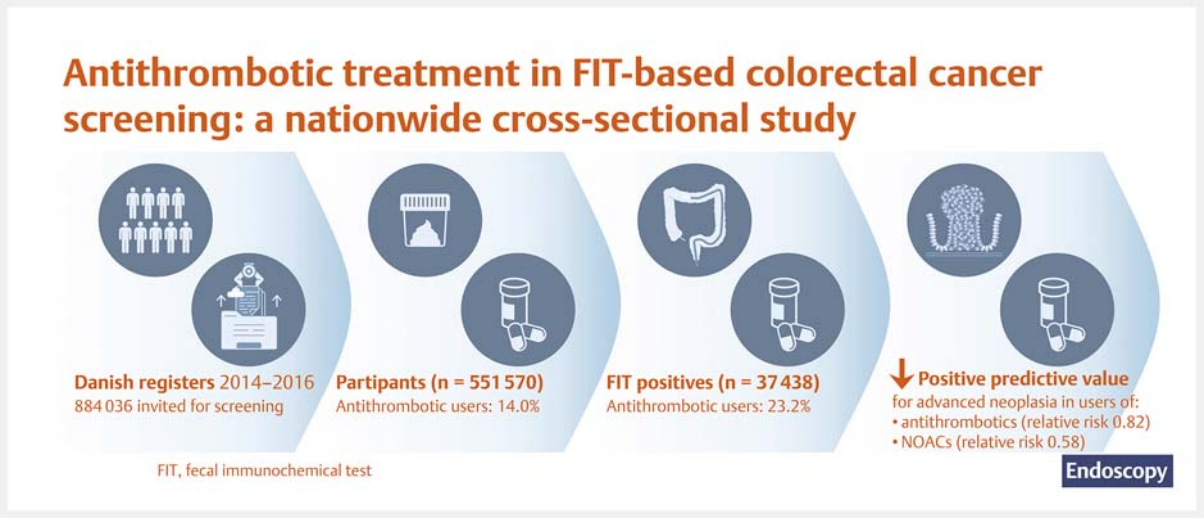
The effect of antithrombotic treatment on the fecal immunochemical test for colorectal cancer screening: a nationwide cross-sectional study

GRAPHICAL ABSTRACT



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ABSTRACT

Background Screening for colorectal cancer (CRC) using the fecal immunochemical test (FIT) has been widely adopted. The use of antithrombotic treatment is increasing in the Western world. This study aimed to assess the effects of antithrombotic treatment on the FIT-based Danish national screening program for CRC.

Methods This was a cross-sectional study of all individuals returning a FIT from 2014 until 2016. The effect of antithrombotic treatment on FIT positivity and the positive predictive value (PPV) were assessed using proportions and multivariable Poisson regression.

Results Of 884 036 invited individuals, we identified 551 570 participants. A positive FIT was observed in 9052 of 77 007 individuals (11.8 %) receiving antithrombotic treatment compared with 28 387 of 474 587 individuals (6.0 %) receiving no treatment. The adjusted relative risk (RR) for a positive FIT was 1.59 (95 %CI 1.56–1.63) for any treatment. Nonvitamin K oral anticoagulants (NOACs) were associated with the largest increase in FIT positivity (adjusted RR 2.40, 95 %CI 2.48–2.54). The proportion of CRC detected at colonoscopy was slightly lower among patients on antithrombotic treatment (6.0 %, 95 %CI 5.5 %–6.6 %) than among treatment-naïve patients (6.4 %, 95 %CI 6.1 %–6.7 %). The PPV for CRC or high risk adenomas was decreased nearly twofold in patients treated with NOAC (adjusted RR 0.58, 95 %CI 0.51–0.66]).

Conclusion Antithrombotic treatment was associated with a decreased PPV in FIT-based CRC screening.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the Western world [1, 2]. Early diagnosis is paramount to ensure the survival of CRC patients, with two main screening strategies being used: (i) sigmoidoscopy, and (ii) fecal occult blood testing. A Cochrane meta-analysis concluded that both methods reduce CRC-specific mortality, promoting the use of either of the two methods [3]. In addition, opportunistic screening with colonoscopy is widely adopted in many high-income countries, particularly in the USA [4].

The number of people treated with anticoagulant or antiplatelet drugs (antithrombotics) is increasing [5]. Treatment options have evolved during the last decades, from mainly acetylsalicylic acid (ASA) and vitamin K antagonists (VKA) to include more potent antiplatelet drugs and nonvitamin K oral anticoagulants (NOACs) [6].

Studies evaluating the effect of antithrombotic treatment on CRC screening have primarily focused on the guaiac-based fecal occult blood test (gFOBT) [7]. The gFOBT is based on the peroxidase activity of heme, and test results are affected by antithrombotic treatment to such a degree that discontinuation is recommended prior to screening [8]. In Denmark and many other European countries, the preferred screening modality has been the fecal immunochemical test (FIT). This preference for FIT over gFOBT is because of its increased sensitivity and specificity, better patient compliance, the lack of dietary restrictions, and, importantly, the ability to continue antithrombotic treatment during testing [9, 10].

The impact of antithrombotic treatment on the efficacy of FIT for CRC detection has been sparsely evaluated [11–16]. The studies have been limited by a relatively low number of participants and they were most often conducted in an opportunistic screening setting. Therefore the effects of antithrombotic treatment on FIT-based CRC screening are still under debate and demand further investigation. We aimed to: (i) assess the effect of any type of antithrombotic treatment on FIT values and FIT positivity; (ii) evaluate the impact on the positive predictive value (PPV) according to the results from the follow-up colonoscopy; and (iii) assess if antithrombotic treatment affected the adherence to the follow-up colonoscopy after a positive FIT.

Methods

Patient involvement

The screening population was not involved in the design or conduct of this research. None of the patients who received antithrombotic treatment were involved in the conceptualization of this study.

Setting and design

National screening for CRC was implemented in Denmark in 2014. Asymptomatic men and women between 50 and 74 years of age were invited to participate. The screening program uses the FIT (Eiken Chemical Co., Ltd.) and eligible individuals receive a test kit for at-home testing. The sample is returned via mail to a regional laboratory, where each sample is analyzed using the OC Sensor DIANA platform. The platform uses latex particles coated with antihuman HbA_0 antibodies, with the presence of hemoglobin being detected by photometric assessment. Individuals who are test positive (hemoglobin concentration ≥ 20 µg/g of feces) are referred to the regional outpatient clinic for a follow-up colonoscopy. Individuals who test negative are subject to biennial testing.

We conducted a nationwide cross-sectional study using data from the first round of CRC screening available from March 2014 until July 2016. The study is in full accordance with the STROBE statement [17] (**Table 1 s**, see online-only Supplementary material).

Data extraction

Data concerning the results of screening were obtained from the Danish Colorectal Cancer Screening Database, which extracts data from existing Danish registers: the Invitation and Administration Module, the Danish National Patient Register, and the Danish Pathology Register. The database does not rely on manual entries and has recently been validated [18]. The results of the screening colonoscopy are recorded as: "colorectal cancer" (regardless of stage); "high risk adenomas" (> 3–4 adenomas found, and/or > 1 cm in size, and/or high grade dysplasia, and/or villous histology); "low risk adenomas" (< 3 adenomas found, all < 1 cm in size, low grade dysplasia, no villous histolo-

gy); or "benign lesions" (angiodysplasia, hyperplastic polyps, etc.).

Data on treatment with anticoagulants and/or antiplatelet agents were collected from the Danish National Health Service Prescription database.

We used a previously described method to identify patients who were receiving antithrombotic treatment at the time of CRC screening [19, 20]. The program ("medicinMacro") is publicly available in the R-package "heaven" [21]. For each compound, the program uses maximal, minimal, and default recommended dosages of each tablet strength and up to five prior prescriptions to calculate treatment periods, which as far as possible provide continuous treatment within the limits of the maximal and minimal recommended dosage. If a treatment window covered the screening date, treatment at the time of screening was assumed.

Co-morbidities were identified from the Danish National Patient Register. The Charlson co-morbidity index was calculated using an adapted version of the method used by Quan et al [22]. The index was based on the international classification of disease codes received 5 years prior to CRC screening. According to the Charlson co-morbidity index, the participants were grouped into three groups (0, 1–2, and ≥ 3).

Participants undergoing screening could have been subject to previous colonoscopies because of symptoms of CRC (lower gastrointestinal hemorrhage, signs of intestinal obstruction, etc.). To correct for this potential confounder, we identified those patients who had received a colonoscopy in the 2 years prior to screening through the National Patient Register.

Statistical analyses

The number of invited individuals according to treatment group is presented. The participation rate was calculated as the number of participants divided by the total number of invited individuals. The FIT positive rate was calculated as the number of FIT positives divided by the total number of participants. The colonoscopy rate was calculated as the number of colonoscopies divided by the number of FIT positives. The PPV of the FIT was calculated as the results of the follow-up colonoscopy divided by the number of subjects undergoing a follow-up colonoscopy according to sex, age, Charlson co-morbidity index, and antithrombotic treatment. The results are presented as proportions with 95 %CIs derived using the exact binomial method and compared using Fisher's exact test.

The effect of antithrombotic treatment on the FIT result was evaluated by multivariable regression. The outcome variable was any value increase of the FIT (discrete variable) or a positive FIT (categorical variable). The exposure variable was the different categories of antithrombotic treatment. Potential confounders were sex, age, and the Charlson co-morbidity index. The confounders were selected because of their association with gastrointestinal hemorrhage. Moreover, treatment with antithrombotics is more prevalent in men, individuals of older age, and those with increasing co-morbidity.

The risk of detecting CRC and/or high grade adenomas on the follow-up colonoscopy was evaluated through multivariable regression. The outcome variables were CRC, and CRC and/or high risk adenomas (combined outcome variable). The exposure variable was the different categories of antithrombotic treatment. Potential confounders were sex, age, and the Charlson co-morbidity index. The confounders were selected because of an increased risk of CRC in men, those of older age, and an association with various co-morbidities included in the Charlson co-morbidity index (e. g. diabetes, liver disease, and certain rheumatological disorders).

The risk of selective adherence to the follow-up colonoscopy after a positive FIT was assessed through multivariable regression. The outcome variable was receiving a follow-up colonoscopy after a positive FIT, adjusted for sex, age, the Charlson co-morbidity index, and previous colonoscopy.

All models were derived from multivariable Poisson regression using the robust variance estimator (STATA command: "glm(... ,family(poisson) vce(robust))"). Age was treated as a continuous variable raised as a second-order polynomial to account for nonlinearity in all models.

All statistical analyses were conducted using STATA version 15.1 (StataCorp. 2017; Stata Statistical Software: release 13; StataCorp LP, College Station, Texas, USA).

Results

We identified 884 036 individuals who received an invitation for screening, of whom 551 570 participated, reflecting a participation rate of 62.4 %. The largest proportion of participants was seen in women, with no co-morbidity and who did not receive antithrombotic treatment (▶ **Table 1**). The proportion of participants on any kind of antithrombotic treatment was 14.0 % (95 %CI 13.9 %–14.1 %). The distribution of antithrombotic treatment according to screening level is shown in **Table 2 s**.

Antithrombotic treatment and FIT positivity

There were 6.8 % of individuals (95 %CI 6.7–6.9) who received a positive FIT (▶ **Table 1**). All types and combinations of antithrombotic treatment led to an increase in FIT positivity, with NOACs, VKAs + antiplatelet agents, and triple therapy in any combination being associated with the largest increase in FIT positivity. The impact of antithrombotic treatment on the risk of a positive FIT, was further evaluated using multivariable Poisson regression (▶ **Fig. 1**). Any treatment was associated with an increased FIT value (▶ **Fig. 1a**). NOAC treatment was associated with a more than twofold increase in FIT positivity (adjusted relative risk [RR] 2.40, 95 %CI 2.48–2.54]). This increase in FIT positivity was only matched by treatment with anticoagulants in combination with antiplatelet drugs. In contrast, the risk of a positive FIT among patients using VKAs alone, or single or double antiplatelet therapy was more modest (▶ **Fig. 1b**).

Antithrombotic treatment and follow-up colonoscopy results

The follow-up colonoscopy revealed CRC in 6.3 % of individuals (▶ **Table 2**). The largest proportion of cancers detected was in men, with increasing age being the predominant risk factor. The lowest proportion of cancers detected was in patients treated with NOAC or combined therapies (VKA + antiplatelet

▶ **Table 1** Characteristics of the invited individuals in the Danish colorectal screening program according to participation, FIT positivity, and adherence to the follow-up colonoscopy.

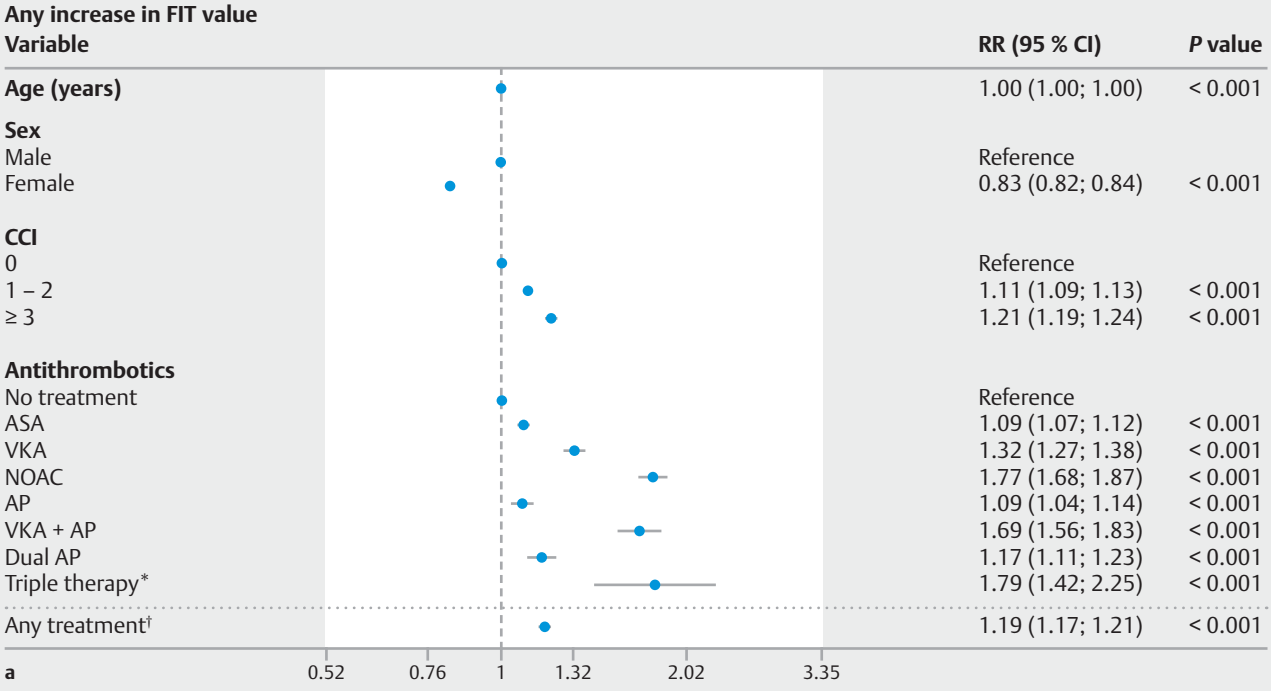
	Total invitees	Participation		FIT positivity		Follow-up colonoscopy	
		n	Rate, % (95 %CI)	n	Rate, % (95 %CI)	n	Rate, % (95 %CI)
Total	**884 036**	**551 570**	**62.4 (62.3–62.5)**	**37 438**	**6.8 (6.7–6.9)**	**31 976**	**85.4 (85.0–85.8)**
Sex							
▪ Male	436 451	255 413	58.5 (58.4–58.7)	20 999	8.2 (8.1–8.3)	18 296	87.1 (86.7–87.6)
▪ Female	447 585	296 157	66.2 (66.0–66.3)	16 439	5.6 (5.5–5.6)	13 680	83.2 (82.6–83.8)
Age, years							
▪ 50–55	322 686	187 087	58.0 (57.8–58.1)	8204	4.4 (4.3–4.5)	6976	85.0 (84.2–85.8)
▪ 56–61	164 104	104 450	63.6 (63.4–63.9)	6147	5.9 (5.7–6.0)	5353	87.1 (86.2–87.9)
▪ 62–67	159 459	107 520	67.4 (67.2–67.7)	8033	7.5 (7.3–7.6)	6993	87.1 (86.3–87.8)
▪ 68–75	237 787	152 513	64.1 (63.9–64.3)	15 054	9.9 (9.7–10.0)	12 654	84.1 (83.5–84.6)
Charlson co-morbidity index							
▪ 0	708 001	450 753	63.7 (63.6–63.8)	27 046	6.0 (5.9–6.1)	23 643	87.4 (87.0–87.8)
▪ 1–2	107 376	63 034	58.7 (58.4–59.0)	6129	9.7 (9.5–10.0)	5007	81.7 (80.7–82.7)
▪ ≥ 3	68 659	37 783	55.0 (54.7–55.4)	4263	11.3 (11.0–11.6)	3326	78.0 (76.7–79.3)
Antithrombotic treatment							
▪ None	734 532	474 567	64.6 (64.5–64.7)	28 386	6.0 (5.9–6.0)	24 544	86.5 (86.1–86.9)
▪ ASA	76 920	44 246	57.5 (57.2–57.9)	4465	10.1 (9.8–10.4)	3727	83.5 (82.3–84.5)
▪ VKA	15 774	9683	61.4 (60.6–62.1)	1368	14.1 (13.4–14.8)	1131	82.7 (80.6–84.5)
▪ NOAC	9552	4601	48.2 (47.2–49.2)	965	21.0 (19.8–22.2)	765	79.3 (76.6–81.8)
▪ Antiplatelet drugs	18 069	9972	55.2 (54.5–55.9)	1026	10.3 (9.7–10.9)	821	80.0 (77.4–82.4)
▪ VKA + antiplatelet	7559	2072	27.4 (26.4–28.4)	442	21.3 (19.6–23.2)	346	78.3 (74.1–82.0)
▪ Dual antiplatelet	18 337	6196	33.8 (33.1–34.5)	734	11.8 (11.1–12.7)	609	83.0 (80.1–85.6)
▪ Triple therapy[1]	3293	233	7.1 (6.2–8.0)	52	22.3 (17.1–28.2)	33	63.5 (49.0–76.4)

ASA, acetylsalicylic acid; VKA, vitamin K antagonist; NOAC, nonvitamin K oral anticoagulant.
[1] Triple therapy relates to any combination of the treatments above involving three drugs.

agent, or triple therapy). The same tendency was seen for advanced adenomas. To evaluate the PPV, we only considered the participants who underwent a follow-up colonoscopy after a positive FIT (n = 31 976). The PPV for CRC and high risk adenomas was only marginally affected by any type of antithrombotic treatment: 35.6 % (95 %CI 34.5 %–36.7 %) in patients receiving antithrombotic treatment, compared with 38.1 % (95 %CI 37.4 %–38.7 %) in treatment-naïve participants.

To evaluate the effect of antithrombotic treatment on all levels of the screening program, the detection rate for CRC and/or high risk adenomas was calculated in all FIT-positive individuals, all participants who returned a FIT, and all invited individuals (▶ **Table 3**). The detection rate after a positive FIT and after a positive FIT + follow-up colonoscopy was highly similar among patients receiving antithrombotic treatment compared with treatment-naïve participants. This suggests that, even though patients receiving antithrombotic treatment were less likely to complete the follow-up colonoscopy, it might not affect the detection of CRC or high risk adenomas. However, when looking at all participants, the proportion of either CRC or high risk adenomas was increased in all patients receiving antithrombotic treatment (▶ **Table 3**). This might suggest that antithrombotic treatment "demasks" some CRCs or premalignant lesions. The observed difference could, however, be a result of age, sex, or co-morbidity because patients receiving antithrombotic treatment are often older and more frail compared with treatment-naïve participants, giving them an increased risk of CRC or high risk adenomas.

To adjust for sex, increasing age, and co-morbidity, multivariable Poisson regression was employed (▶ **Fig. 2**). Increasing age and male sex were still associated with an increased risk of detecting CRC and/or high risk adenomas at the follow-up colonoscopy, regardless of antithrombotic treatment (▶ **Fig. 2a,b**). Patients on antithrombotic treatment had a reduced risk of



▶ **Fig. 1** The relative risks (RRs) and 95 %CIs, generated by multivariable Poisson regression, associated with antithrombotic treatment at the time of the fecal immunochemical test (FIT) among 551 570 screening participants are shown for the different types of antithrombotic treatment and the potential confounders in terms of: **a** any increase in the FIT value; **b** FIT positivity.
CCI, Charlson co-morbidity index; ASA, acetylsalicylic acid; VKA, vitamin K antagonist; NOAC, nonvitamin K oral anticoagulant; AP, antiplatelet therapy.
* Triple therapy relates to any combination of the treatments above involving three drugs.
† This estimate reflects the result with antithrombotic treatment treated as a dichotomous variable adjusted for age, sex, and CCI.

being diagnosed with CRC or high risk adenomas during the follow-up colonoscopy (adjusted RR 0.82, 95 %CI 0.79–0.85). The detection of CRC or high risk adenomas was substantially reduced in patients using NOACs (adjusted RR 0.58, 95 %CI 0.51–0.66) (▶ **Fig. 2b**).

As stated earlier, the crude detection of CRC or high risk adenomas was elevated in all patients receiving antithrombotic

▶ **Table 2** Colonoscopy results according to antithrombotic treatment and patient characteristics.

	Colorectal cancer		High risk adenomas		Low risk adenomas		Benign lesions		Clean colon		Missing	
	n	% (95 %CI)	n	% (95 %CI)	n	% (95 %CI)	n	% (95 %CI)	n	% (95 %CI)	n	% (95 %CI)
Total	2027	5.4 (5.2–5.6)	9959	26.6 (26.2–27.1)	4189	11.2 (10.9–11.5)	1185	3.2 (3.0–3.3)	14616	39.0 (38.5–39.5)	5462	14.6 (14.2–15.0)
Sex												
▪ Male	1217	5.8 (5.5–6.1)	6454	30.7 (30.1–31.4)	2578	12.3 (11.8–12.7)	695	3.3 (3.1–3.6)	7532	35.0 (34.3–35.7)	2703	12.9 (12.4–13.3)
▪ Female	810	4.9 (4.6–5.3)	3505	21.3 (20.7–22.0)	1611	9.8 (9.3–10.3)	490	3.0 (2.7–3.3)	7264	44.2 (43.4–45.0)	2759	16.8 (16.3–17.4)
Age, years												
▪ 50–64	204	2.5 (2.2–2.8)	1641	20.0 (19.1–20.9)	816	10.0 (9.3–10.6)	185	2.3 (1.9–2.6)	656	50.3 (49.2–51.4)	1228	15.0 (14.2–15.8)
▪ 55–61	267	4.3 (3.8–4.9)	1664	27.1 (26.0–28.2)	758	12.3 (11.5–13.2)	149	2.4 (2.1–2.8)	399	40.9 (39.7–42.2)	794	12.9 (12.1–13.8)
▪ 62–67	457	5.7 (5.2–6.2)	2334	29.1 (28.1–30.1)	953	11.9 (11.2–12.6)	274	3.4 (3.0–3.8)	477	37.0 (36.0–38.1)	1040	12.9 (12.2–13.7)
▪ 68–75	1099	7.3 (6.9–7.7)	4320	28.7 (28.0–29.4)	1662	11.0 (10.5–11.6)	577	3.8 (3.5–4.2)	1033	33.2 (32.4–33.9)	2400	15.9 (15.4–16.5)
Charlson comorbidity index												
▪ 0	1532	5.7 (5.4–5.9)	7463	27.6 (27.1–28.1)	3099	11.4 (11.1–11.8)	807	3.0 (2.8–3.2)	10742	4.0 (3.9–4.0)	3403	12.6 (12.2–13.0)
▪ 1–2	285	6.1 (4.1–5.2)	1541	25.1 (24.1–26.2)	651	10.6 (9.9–11.4)	211	3.4 (3.0–3.9)	2319	3.8 (3.7–3.9)	1122	18.3 (17.3–19.2)
▪ ≥3	210	4.9 (4.3–5.6)	955	22.4 (21.1–23.7)	439	10.3 (9.4–11.2)	167	3.9 (3.3–4.5)	1555	3.6 (3.5–3.8)	937	22.0 (20.7–23.3)
Antithrombotic treatment												
▪ None	1578	5.6 (5.3–5.8)	7762	27.3 (26.8–27.8)	3211	11.3 (10.9–11.7)	808	2.9 (2.7–3.0)	11185	39.4 (38.8–40.0)	3842	13.5 (13.1–13.9)
▪ ASA	249	5.6 (4.9–6.3)	1084	24.3 (23.0–25.6)	490	11.0 (10.1–11.9)	163	3.7 (3.1–4.2)	1741	39.0 (37.6–40.4)	738	16.5 (15.5–17.7)
▪ VKA	65	4.8 (3.7–6.0)	377	27.6 (25.2–30.0)	153	11.2 (9.6–13.0)	78	5.7 (4.5–7.1)	458	33.5 (31.0–36.1)	237	17.3 (15.4–19.4)

▶ **Table 2** (Continuation)

	Colorectal cancer		High risk adenomas		Low risk adenomas		Benign lesions		Clean colon		Missing	
▪ NOAC	25	2.6 (1.7–3.8)	170	17.6 (15.2–20.2)	109	11.3 (9.4–13.5)	43	4.5 (3.2–6.0)	418	43.3 (40.1–46.5)	200	20.7 (18.2–23.4)
▪ Anti-platelet	57	5.6 (4.2–7.1)	273	26.6 (23.9–29.4)	90	8.8 (7.1–10.7)	46	4.5 (3.3–5.9)	355	34.6 (31.7–37.6)	205	20.0 (17.6–22.5)
▪ VKA + antiplatelet	16	3.6 (2.1–5.8)	94	21.3 (17.5–25.4)	47	10.6 (7.9–13.9)	15	3.4 (1.9–5.5)	174	39.4 (34.8–44.1)	96	19.6 (18.0–25.9)
▪ Dual antiplatelet	36	4.9 (3.5–6.7)	189	25.8 (22.6–29.1)	85	11.6 (9.4–14.1)	25	3.4 (2.2–5.0)	274	37.3 (33.8–40.9)	125	17.0 (14.4–19.9)
▪ Triple therapy[1]	1	1.9 (0.0–10.3)	10	19.2 (9.6–32.5)	4	7.7 (2.1–18.5)	7	13.5 (5.6–25.8)	11	21.2 (11.1–34.7)	19	36.5 (23.6–51.0)

ASA, acetylsalicylic acid; VKA, vitamin K antagonist; NOAC, nonvitamin K oral anticoagulant.
[1] Triple therapy relates to any combination of the treatments above involving three drugs.

treatment who returned a FIT (regardless of the result). According to the multivariable analysis, the elevated CRC detection in patients receiving any type of antithrombotic treatment could be explained by age, sex, and co-morbidity (▶ **Fig. 2c**). However, the risk of detecting either CRC or high risk adenomas remained higher in patients treated with VKAs, NOACs, or VKAs + NOACs after adjustment (▶ **Fig. 2 d**). This indicates that treatment with anticoagulants might "demask" at least some high risk adenomas through FIT-based CRC screening.

Selective adherence

The proportion of participants completing the follow-up colonoscopy after a positive FIT was lowest among participants of female sex, in the oldest age quartile, with the highest Charlson co-morbidity index, and in those receiving any kind of antithrombotic treatment (▶ **Table 1**).

The proportion of patients who had received a colonoscopy within 2 years prior to their screening among the FIT positive individuals was 6.7 % (95 %CI 6.2 %–7.3 %) in patients receiving antithrombotic treatment compared with 4.3 % (95 %CI 4.3 %–4.5 %) in participants not receiving any treatment ($P < 0.001$). In this regard, it is noteworthy that 17.9 % (95 %CI 17.1 %–18.7 %) of patients receiving antithrombotic treatment never underwent the follow-up colonoscopy, compared with 13.5 % (95 %CI 13.1 %–13.9 %) of treatment-naïve participants (▶ **Table 1**). Among patients who had undergone a colonoscopy within 2 years prior to screening, the proportion was 37.8 % (95 %CI 34.0 %–41.8 %) in patients receiving any type of antithrombotic treatment and 33.9 % (95 %CI 31.1 %–36.7 %) among treatment-naïve patients ($P = 0.11$). Multivariable analysis of the risk of selective adherence to the follow-up colonoscopy revealed the same result (**Fig. 1 s**). There was a statistically nonsignificant interaction between previous colonoscopy and antithrombotic treatment ($P = 0.72$), and adjustment for previous colonoscopy in the multivariable analyses did not alter any of the estimates, suggesting no effect modification. Most antithrombotic treatment regimens therefore seem to decrease the chance of completing the follow-up colonoscopy after a positive FIT, regardless of age, co-morbidity, and prior colonoscopy.

Discussion

The detection of occult blood in stool samples is the core of the Danish screening program for CRC. Not surprisingly, we showed that the test is significantly affected by treatment with antithrombotics.

An important finding of our study was that, regardless of age or sex, treatment with NOACs increased the risk of a positive FIT more than twofold. It is well known that antithrombotic treatment increases the risk of gastrointestinal hemorrhage [23, 24]. This is especially the case for NOACs, as they have been shown to more than double the risk of gastrointestinal hemorrhage compared with VKAs (hazard ratio 2.18, 95 %CI 1.83–2.59) [25]. It has even been proposed that treatment with NOACs could unmask CRCs, making them detectable through occult blood testing [25].

▶ **Table 3** Crude detection rates of colorectal cancer (CRC) and high risk adenoma (HRA) according to different levels of the screening program.

	Detection rate/colonoscopy, %[1]		Detection rate/positive FIT, %[2]		Detection rate/1000 FITs performed[3]		Detection rate/1000 invited participants[4]	
	CRC	CRC/HRA	CRC	CRC/HRA	CRC	CRC/HRA	CRC	CRC/HRA
Total	6.3	37.5	5.4	32.0	3.7	21.7	2.4	14.0
Sex								
▪ Male	6.7	41.9	5.8	36.5	4.8	30.0	2.9	18.2
▪ Female	5.9	31.5	4.9	26.3	2.7	14.6	1.9	10.0
Age, years								
▪ 50–55	2.9	26.5	2.5	22.5	1.1	9.9	0.7	6.0
▪ 56–61	5.0	36.1	4.3	31.4	2.6	18.5	1.7	12.1
▪ 62–67	6.5	39.9	5.7	34.7	4.3	26.0	3.0	18.1
▪ 68–75	8.7	42.8	7.3	36.0	7.2	35.5	4.8	23.6
Charlson co-morbidity index								
▪ 0	6.5	38.1	5.7	33.3	3.4	20.0	2.3	13.1
▪ 1–2	5.7	36.5	4.7	29.8	4.5	29.0	2.8	17.7
▪ ≥3	6.3	35.0	4.9	27.3	5.6	30.8	3.2	17.6
Antithrombotic treatment								
▪ None	6.4	38.1	5.6	32.9	3.3	19.7	2.2	13.1
▪ ASA	6.7	35.8	5.6	29.9	5.6	30.1	3.4	18.3
▪ VKA	5.8	39.1	4.8	32.3	6.7	45.6	4.2	29.0
▪ NOAC	3.3	25.5	2.6	20.2	5.4	42.4	2.9	21.6
▪ Antiplatelet drugs	6.9	40.2	5.7	32.2	5.7	33.1	3.5	19.1
▪ VKA + antiplatelet	4.6	31.8	3.6	24.9	7.7	5.31	3.0	16.7
▪ Dual antiplatelet	5.9	37.0	4.9	20.7	5.8	3.63	2.2	13.3
▪ Triple therapy[5]	3.0	33.3	1.9	32.0	4.3	4.72	1.2	7.6

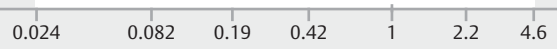
ASA, acetylsalicylic acid; VKA, vitamin K antagonist; NOAC, nonvitamin K oral anticoagulant.
[1] Reflects the positive predictive value of the FIT with adherence to the follow-up colonoscopy (n = 31 976).
[2] Reflects the detection of CRC or HRA in all the participants who received a positive FIT result, including those individuals who did not undergo the follow-up colonoscopy (n = 37 438).
[3] Reflects the detection rate in the total population of screened individuals (n = 551 570).
[4] Reflects the detection rate in the total population of invited individuals (n = 884 036).
[5] Triple therapy relates to any combination of the treatments above involving three drugs.

The fact that NOAC treatment leads to an increased number of FIT positives is in line with a recent large Norwegian study [14]. The authors found that the PPV for CRC was reduced to 0.9 % in patients treated with NOACs, compared with a PPV of 6.8 % in matched nonusers (approximately a sevenfold decrease). This marked decrease in PPV was shown only partly in our study, with the risk of detecting CRC being reduced by only threefold (RR 0.37, 95 %CI 0.25–0.56). The reason for this marked difference between the Norwegian and Danish populations can only be speculated. Differences in patient allocation to NOAC treatment, along with potential lifestyle factors, might have had an impact.

To date, no study has found any support for the discontinuation of antithrombotic treatment prior to FIT-based CRC screening. In 2009, Levi et al. evaluated the effect of low dose aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), and anticoagulants on the FIT screening method in 1221 patients undergoing colonoscopy [11]. Each patient delivered three FITs and received a subsequent colonoscopy. Treatment with aspirin/NSAIDS led to an increase in sensitivity (66.7 % in users vs. 46.5 % in nonusers), but without a change in specificity. The difference was however not statistically significant. Bujanda et al. showed in 2014 that the positive rate for CRC using the FIT was 9.3 % in the group using anticoagulants compared with 6.2 % in the control group. Moreover, the PPV for advanced neoplasia was 47.6 % in the group on anticoagulant treatment compared with 50.4 % in the control group; however, the difference was not statistically significant [12].

CRC in FIT-positive individuals undergoing colonoscopy

Variable	RR (95 % CI)	*P* value
Age (years)	1.00 (1.00; 1.00)	< 0.001
Sex		
Male	Reference	
Female	0.89 (0.82; 0.97)	0.008
CCI		
0	Reference	
1 – 2	0.83 (0.73; 0.94)	0.004
≥ 3	0.83 (0.72; 0.96)	0.014
Antithrombotics		
No treatment	Reference	
ASA	0.85 (0.74; 0.97)	0.014
VKA	0.69 (0.54; 0.88)	0.003
NOAC	0.40 (0.27; 0.59)	< 0.001
AP	0.94 (0.72; 1.22)	0.650
VKA + AP	0.55 (0.34; 0.89)	0.015
Dual AP	0.82 (0.60; 1.13)	0.234
Triple therapy*	0.34 (0.05; 2.37)	0.275
Any treatment†	0.77 (0.69; 0.85)	< 0.001



a

CRC and/or HRA in FIT-positive individuals undergoing colonoscopy

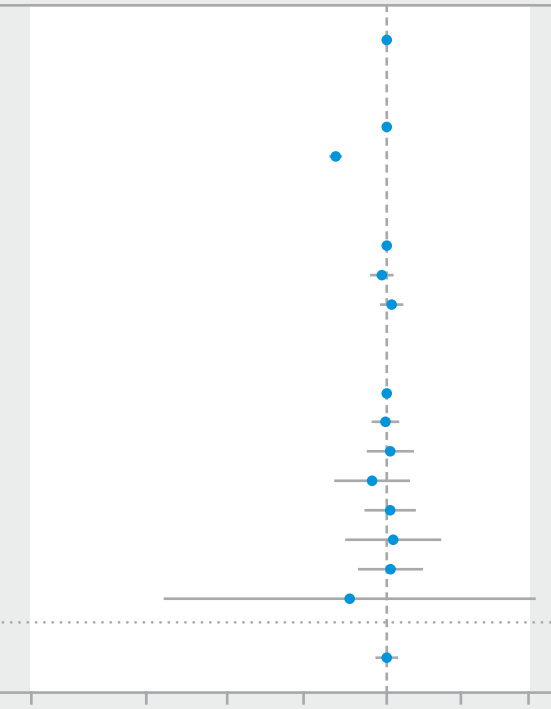
Variable	RR (95 % CI)	*P* value
Age (years)	1.00 (1.00; 1.00)	< 0.001
Sex		
Male	Reference	
Female	0.75 (0.73; 0.77)	< 0.001
CCI		
0	Reference	
1 – 2	0.94 (0.90; 0.98)	0.007
≥ 3	0.86 (0.81; 0.90)	< 0.001
Antithrombotics		
No treatment	Reference	
ASA	0.83 (0.79; 0.87)	< 0.001
VKA	0.88 (0.81; 0.95)	0.001
NOAC	0.58 (0.51; 0.66)	< 0.001
AP	0.96 (0.89; 1.05)	0.406
VKA + AP	0.70 (0.60; 0.81)	< 0.001
Dual AP	0.88 (0.80; 0.98)	0.018
Triple therapy*	0.71 (0.44; 1.15)	0.163
Any treatment†	0.82 (0.79; 0.85)	< 0.001

b

▶ **Fig. 2** The relative risks (RRs) and 95 %CIs, generated by multivariable Poisson regression, associated with antithrombotic treatment and the detection of: **a, c** colorectal cancer (CRC); **b, d** CRC or high risk adenoma (HRA) in: **a, b** participants who received a positive FIT result and underwent a follow-up colonoscopy (n = 31 976); **c, d** all participants who returned their FIT (n = 551 570).
CCI, Charlson co-morbidity index; ASA, acetylsalicylic acid; VKA, vitamin K antagonist; NOAC, nonvitamin K oral anticoagulant; AP, antiplatelet therapy.
* Triple therapy relates to any combination of the treatments above involving three drugs.
† This estimate reflects the result with antithrombotic treatment treated as a dichotomous variable adjusted for age, sex, and CCI.

CRC in all individuals who returned a FIT

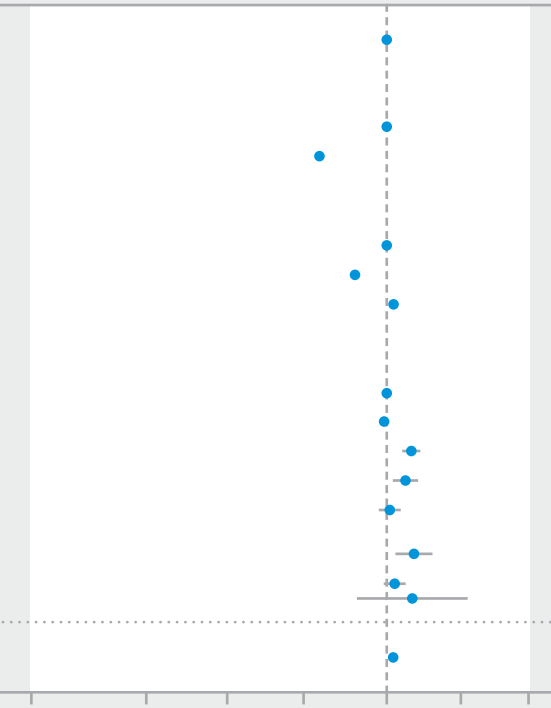
Variable	RR (95 % CI)	*P* value
Age (years)	1.00 (1.00; 1.00)	< 0.001
Sex		
Male	Reference	
Female	0.59 (0.54; 0.65)	< 0.001
CCI		
0	Reference	
1 – 2	0.96 (0.84; 1.10)	0.539
≥ 3	1.06 (0.91; 1.23)	0.457
Antithrombotics		
No treatment	Reference	
ASA	0.99 (0.86; 1.14)	0.892
VKA	1.04 (0.81; 1.34)	0.736
NOAC	0.87 (0.58; 1.29)	0.481
AP	1.04 (0.79; 1.36)	0.804
VKA + AP	1.08 (0.66; 1.78)	0.756
Dual AP	1.04 (0.74; 1.45)	0.831
Triple therapy*	0.68 (0.10; 4.83)	0.700
Any treatment†	1.00 (0.89; 1.12)	0.998



c

CRC and/or HRA in all individuals who returned a FIT

Variable	RR (95 % CI)	*P* value
Age (years)	1.00 (1.00; 1.00)	< 0.001
Sex		
Male	Reference	
Female	0.50 (0.48; 0.52)	< 0.001
CCI		
0	Reference	
1 – 2	1.10 (1.04; 1.16)	< 0.001
≥ 3	1.09 (1.03; 1.16)	0.006
Antithrombotics		
No treatment	Reference	
ASA	0.98 (0.92; 1.04)	0.473
VKA	1.33 (1.21; 1.46)	< 0.001
NOAC	1.26 (1.10; 1.46)	0.001
AP	1.07 (0.96; 1.20)	0.242
VKA + AP	1.37 (1.14; 1.65)	0.001
Dual AP	1.13 (0.99; 1.29)	0.074
Triple therapy*	1.35 (0.76; 2.41)	0.301
Any treatment†	1.08 (1.03; 1.13)	0.002



d

Most recently, in 2021, a population-based Korean study was conducted by Jung et al. The authors analyzed more than 5 million participants, of whom 786 733 were receiving antiplatelet treatment and 19 569 were receiving VKAs. Antiplatelet treatment reduced the PPV of FIT (RR 0.83 [95 %CI 0.78–0.88]); however, treatment with VKAs did not (RR 0.92 [95 %CI 0.64–1.34]) [16]. The results regarding antiplatelet treatment are similar to our findings; however, the results regarding VKAs do not match the reduction in PPV for CRC found in our study (adjusted RR 0.68 [95 %CI 0.53–0.87]). The authors argued that VKAs have limited intraluminal anticoagulant activity in the gastrointestinal tract. Our results do not support this conclusion. One explanation could be the fact that, in the Korean population, treatment with VKA after ischemic stroke only achieves the targeted therapeutic range 44.6 % of the time, with 41.7 % having an international normalized ratio (IVR) < 2.0 [26]; in Denmark, the targeted therapeutic range is achieved 69.3 % of the time [27]. The Korean study was also limited by not including any patients receiving NOAC treatment, as the study period was from 2009 until 2011 [16].

Our study showed that all antithrombotics decreased the PPV of FIT, and NOAC treatment resulted in a marked reduction in FIT performance. NOACs did however seem to "demask" at least some high risk adenomas, and no recommendation regarding antithrombotic discontinuation prior to FIT-based screening can be made using our present data.

A surprising discovery was that the rate of participants lacking a follow-up colonoscopy was higher in patients receiving antithrombotic treatment compared with treatment-naïve participants. This difference is crucial, as some of the participants lacking a colonoscopy could have been diagnosed with CRC or high risk adenomas. The reason for this difference may be attributable to either patient- or provider-related factors. We have made an estimate as to the effect of prior colonoscopy, which in part could explain some of the difference, although adjustment for prior colonoscopy did not alter the immediate conclusions. Earlier studies have suggested that most failures to undergo a subsequent endoscopic evaluation following a positive stool-based screening test are patient related (57 %); a lower proportion are provider related, but mostly due to a lack of referral (18 %–22 %) [28]. Patients receiving antithrombotic treatment are older and more frail, which may play a part in both explanations [29, 30].

The major strength of the current study is the use of nationwide data from the first 2 years of CRC screening in Denmark. The adherence rate of ~60 % is substantial and matches the adherence rate in other Western countries [31, 32]; however, the fact that not everyone adheres to screening in the first place might introduce selection bias. Participants who accept an invitation for FIT-based screening usually have more health-seeking behavior and might not represent the entire population. Our data show that any type of antithrombotic treatment reduces the participation rate for FIT-based CRC screening. NOAC treatment led to a reduction in participation rate by approximately 25 %, even after adjustment for sex and age (data not shown). This shows that antithrombotic treatment (especially with NOACs) also contributes selection bias and, as such, the results should be interpreted with some caution.

In addition, the study is limited by a lack of information surrounding CRC stage and other important aspects, such as socioeconomic status, which could have shed light on the factors influencing the differences in completion of the screening colonoscopy. Moreover, we defined patients as being on antithrombotic treatment according to the collection of prescriptions prior to screening. It is recommended that patients continue their antithrombotic treatment during screening; however, we have no information as to whether some of the patients discontinued treatment prior to screening. Nevertheless, this type of misclassification would most often lead to a type II error and thereby an underestimate of the effect of antithrombotic treatment on the FIT. The fact that there were more FIT positive results in patients on antithrombotic treatment demonstrates the correlation between apparent use and actual use of antithrombotic treatment. Last, a large caveat is the lack of information surrounding the participants with a negative FIT. As these patients never underwent colonoscopy, it was not possible to draw any conclusions as to the negative predictive value of the FIT according to antithrombotic treatment.

All the limitations listed above preclude us from making any conclusions as to the causal relationship between antithrombotic treatment and FIT positivity, and which lesions might be "demasked" at follow-up colonoscopy. We can only make inference as to the association between antithrombotic treatment and the risk of a positive FIT and the PPV in the first round of CRC screening in Denmark. The association might be altered through subsequent rounds of screening as more individuals are subjected to biennial testing. The evaluation of effect on different screening rounds was however not possible using our present data. Future studies should evaluate whether any of the limitations mentioned above could affect any part of the screening program using the FIT.

In conclusion, patients receiving antithrombotic treatment are at increased risk of a positive FIT and at a marginally decreased risk of CRC or high risk adenoma detection at subsequent colonoscopy. Treatment with NOACs is increasing and the fact that it leads to a more than twofold increase in FIT positive results could highlight the need for other adjunctive testing (using novel blood- or stool-based biomarkers), both to decrease the number of colonoscopy-related complications and to lessen the burden on colonoscopy units [33, 34]. Future studies should address this issue when these biomarkers are being employed in clinical practice.

Competing Interests

The authors declare that they have no conflict of interest.

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