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Prevalence of Significant Neoplasia in FOBT-Positive Patients on Warfarin Compared With Those Not on Warfarin

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Abstract

OBJECTIVES—The fecal occult blood test (FOBT) is widely used for colorectal cancer screening. However, the impact of warfarin use on FOBT sensitivity and specificity remains unclear. This study compares the relative risk of neoplasia in FOBT-positive patients stratified by warfarin use.

METHODS—The Clinical Outcomes Research Initiative database was used to identify patients with positive FOBT as the only indication for colonoscopy during 2005–2006. Patients were categorized on the basis of documented warfarin status within a 30-day period before FOBT. We compared the demographics and prevalence of significant colon findings (defined as polyp > 9 mm or suspected malignant tumor) among the two groups. After adjusting for confounding variables, logistic regression was used to estimate the odds ratio of significant findings in warfarin-positive vs. warfarin-negative patients.

RESULTS—Of 10,266 patients with positive FOBT, 372 used warfarin, 9,265 did not use warfarin, and 629 were excluded because of missing warfarin status. Warfarin-positive patients were more likely male (65 vs. 50%; $P< 0.0001$), Caucasian (88 vs. 80%; $P< 0.0001$), and veterans (53 vs. 33%; $P< 0.0001$). The prevalence of a significant finding was greater in the warfarin group, 16 vs. 11.4% ($P< 0.01$). After adjusting for age and sex, the relative risk of significant colon findings among warfarin-positive patients was not significantly different from warfarin-negativepatients (odds ratio 1.1, 95% confidence interval: 0.81–1.44).

CONCLUSIONS—No increased risk for significant colonic findings among FOBT-positive patients according to warfarin use was identified. These findings suggest that continuing warfarin before FOBT will not affect the positive predictive value of this screening test.

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CONFLICT OF INTEREST

Guarantor of the article: Judy F. Collins, MD.

Specific author contributions: Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the paper, and critical revision of the paper for important intellectual content: LuLu Iles-Shih; study concept and design, analysis and interpretation of data, drafting of the paper, study supervision, and critical revision of the paper for important intellectual content: Judy F. Collins; analysis and interpretation of data, statistical analysis, and technical support: Jennifer L. Holub; critical revision of the paper for important intellectual content, analysis and interpretation of data, and study supervision: David A. Lieberman.

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INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of death from cancer in the United States for both men and women (1). Screening for CRC has been shown to reduce mortality from colon cancer (2,3), and fecal occult blood testing (FOBT) reduces mortality rate (4). The latest set of guidelines from the American Cancer Society, the American Gastroenterological Association, and the United States Preventive Task Force recommend FOBT to detect cancer, or structural tests such as colonoscopy, flexible sigmoidoscopy, barium enema, or computed tomography colonography to detect polyps and early cancer (5–7), with the goal of cancer prevention. Of the possible screening tests in 2005, Hemoccult II FOBT was the most widely used FOBT for CRC screening in the United States (8), and is the only CRC screening test for which there is evidence of efficacy from prospective, randomized controlled trials (5).

Hemoccult II FOBT is a guaiac-based test. To optimize the performance of the test, it is recommended that patients eliminate specified items from their diet for 3 days and to avoid non-steroidals for 7 days before testing (9). Although not officially recommended, it has been observed that many primary care physicians will also discontinue warfarin before the collection of stool specimens for occult blood testing on the basis of the assumption that warfarin would increase the false-positive rate of FOBTs (10–12).

Warfarin is an anticoagulant that is associated with an increased risk of overt gastrointestinal (GI) bleeding (13,14), and is one of the top 200 medications prescribed in the United States (15,16). However, the manufacturer of the Hemoccult II test and current CRC screening guidelines (3,6,7) do not address whether warfarin should be discontinued before FOBT. In clinical practice, 15.9% of primary care physicians (10), 32.0% of gastroenterologists (11), and 10.1% of internal medicine residents (12) report that they discontinue anticoagulants before FOBT. On the basis of observation, many centers recommend stopping warfarin for several days before obtaining the FOBT, or referring these patients for flexible sigmoidoscopy as a screening test for CRC instead of FOBT.

The impact of warfarin on FOBT test sensitivity and specificity remains uncertain, and previous work has suggested that warfarin may increase the rate of false-positive examinations and reduce the positive predictive value of FOBT. Bini *et al.* (17) evaluated 210 patients on warfarin at a New York Veterans Affairs (VA) Medical Center compared with 210 age- and sex-matched individuals not on anticoagulants who were referred for colonoscopy to evaluate a positive FOBT result. They found no difference in the positive predictive value of FOBT.

Our primary objective was to determine the prevalence of significant neoplasia in patients with positive FOBT on warfarin compared with those not on warfarin at the time of colonoscopy. The end points of the analysis were polyps >9mm or suspected malignancy. Patients were stratified by age, sex, and practice site in a large cross-sectional database.

METHODS

The Clinical Outcomes Research Initiative (CORI) represents a consortium of GI practices, which use a computerized endoscopic procedure report generator to produce their endoscopic reports. During the study period, the CORI database contained data on > 1.7 million procedures from > 400 participating endoscopists from 68 adult practice sites within the United States. Practice sites include private practice (78% of colonoscopy reports), academic sites (10%), and VA sites (11%). Reports from each site are transmitted electronically to a central data repository and merged for analysis.

All patient and physician identifiers are removed from the data file before transmission from the local site to protect both patient and physician confidentiality. The data are subjected to quality control checks to identify missing fields. Internalized quality control checks include parameters for size descriptions and drug dosage. After completion of quality control checks, data from all sites are merged in the data repository for analysis. Site compliance is assessed annually. Sites provide record counts of procedures, which are compared with procedure counts in the data repository. If sites fail to record >95% of endoscopic reports using the CORI software, they are notified to improve compliance. Failure to improve compliance results in the exclusion of the site's data from analysis.

Data were prospectively collected during 2004 and 2005. Patients were included in this analysis if they were 18 years of age and received colonoscopy for positive FOBT with or without indications of routine screening, family history of polyps, or a family history of CRC. Patients were excluded if they had any other indication for colonoscopy, such as the presence of lower GI symptoms, hematochezia, iron deficiency anemia, or change in bowel habits.

End point

Subjects underwent screening examinations for colorectal neoplasia. We defined the finding of significant polyps as our key end point. As pathology results are provided only for 23.1% of colonoscopy reports, we used the finding of one or more polyps > 9 mm and/or a suspected malignant tumor as a surrogate end point for the prevalence of advanced neoplasia in the cohorts. The validity of the surrogate end point was evaluated in a previous analysis (18).

Analysis

Patients were categorized on the basis of their documented warfarin status within 30 days of examination. The prevalence of significant polyps was compared for the two groups. All analyses were performed using SAS v9.1 software (SAS Institute, Cary, NC). Pearson's 2 test was used to compare proportions. In instances, with small cell sizes, Fisher's exact test was used for comparison. Multivariate logistic regression was performed to determine the risk of a significant colonoscopy finding for positive FOBT patients on warfarin compared with positive FOBT patients not on warfarin while controlling for potential confounders. Potential confounders in the model included age, sex, race/ethnicity, family history of CRC or polyps, and practice type (Community/VA/ Academic). Variables were retained in the model if they showed confounding with warfarin status. Adjusted odds ratios and 95% confidence intervals are presented.

RESULTS

Between 2005 and 2006, 298,949 colonoscopy procedures were reported to the CORI database in 288,638 unique patients. A total of 10,266 patients with the indication of positive FOBT (with or without screening and family history indications) were entered into the CORI. Of these, 629 patients were missing warfarin status and thus were excluded from the analysis. The remaining 9,637 patients were included in the final analysis.

Warfarin use was reported in 372 patients (3.9%). More than half of these patients were from VA practices (Table 1). Patients on warfarin were more likely to be male (65 vs. 50%; $P<0.0001$, even when VA sites were excluded), Caucasian (88 vs. 80%; $P<0.0001$), and veterans (53 vs. 33%; $P<0.0001$), compared with those not on warfarin. Overall, the prevalence of a significant finding was greater in the warfarin group, 16 vs. 11.4% ($P=0.005$) (Table 2). After adjustment for age and sex, there was no difference in the odds

ratio of significant findings in patients with and without warfarin (odds ratio 1.1, 95%, confidence interval: 0.81–1.44).

DISCUSSION

Using a diverse cross-sectional database, we showed that the use of warfarin did not change the odds of finding significant colonic neoplasia in patients with positive FOBT. Our findings are in agreement with two other studies regarding the performance characteristics of guaiac FOBT and immunochemical FOBT in patients on warfarin or warfarin and nonsteroidal anti-inflammatory drugs,respectively (17,19). A smaller study by Bini *et al.* (17) showed that the positive predictive value of guaiac FOBT for GI lesions in patients taking warfarin was similar to that in an age- and sex-matched group of subjects with a positive FOBT who were not taking oral anticoagulants. Levi *et al.*(19) showed a trend toward increased sensitivity but no change in the specificity of immunochemical FOBT in asymptomatic patients on nonsteroidal antiinflammatory drugs or warfarin for finding advanced neoplasia or CRC.

The results of our study are clinically important because warfarin is the most commonly prescribed oral vitamin K antagonist in the United States with ~2.5 million patients receiving it in 2005–2008 (13,15,16,20). Warfarin remains one of the top 200 medications prescribed in the United States (15,16), and is effective for the treatment of thromboembolic disorders (21). Therefore, continuing anticoagulant therapy during FOBT potentially reduces the small but finite risk of stroke or other thromboembolic complications associated with temporarily stopping warfarin (22).

Warfarin-associated GI hemorrhage is an important cause of morbidity and mortality (14), and the frequency and etiology of acute GI hemorrhage have been well described in patients on anticoagulation therapy (23–28). However, there are few studies evaluating occult GI bleeding in patients on warfarin (17). There are three small studies looking at fecal hemoglobin in patients with occult GI blood loss on warfarin. Greenberg *et al.* (29) measured fecal hemoglobin concentration in a small population of 25 patients on warfarin and found no increase in GI blood loss. Similarly, Prichard*et al.* (30) found that warfarin had no effect on upper GI blood loss when administered alone or in combination with aspirin. However, Blackshear *et al.* (31) found that patients taking warfarin alone or in combination with aspirin were more likely to have occult GI blood loss than were patients taking aspirin alone, and quantitative fecal hemoglobin levels were highest in the combination group. Bini *et al.* (17) suggested that warfarin use may actually improve the rate of detection for colonic neoplasia. However, because of the concern that warfarin may reduce the positive predictive value of FOBT, some primary care providers stop warfarin during FOBT (10–12).

Our study evaluated colonoscopy outcomes of a cohort of asymptomatic FOBT-positive patients on or off warfarin before colonoscopy. The strengths of this study include the large sample size, the inclusion of a diverse patient population from private practices, academic sites and the Department of VA sites, and the focus on otherwise asymptomatic patients. However, our study has some limitations. Race/ethnicity information was provided by the endoscopist and therefore subject to misclassification. The small number of warfarin takers limits the conclusions. In addition, we could not verify the dosage of warfarin or the range of target international normalized ratio based on the CORI report. Whether the dosage of warfarin or the range of target international normalized ratio has an impact on the diagnostic yield of FOBT is also unknown and is another limitation of this study. This is another limitation of the study. We used a surrogate end point for advanced neoplasia (polyps sized > 9 mm or suspected malignancy), which we have shown to be related to the actual rate of histologically proven advanced neoplasia in a screening cohort. However, estimates of the

polyp size at endoscopy could be subject to error, based on previous work (32,33). In addition, the CORI consortium may not be representative of endoscopic practice in the United States, even though it includes a broad range of community-based practices. During this study period, the standard protocol for guaiac FOBT was the development of nonrehydrated Hemoccult II cards. However, we could not verify this practice for every site. Our results are also limited to the positive predictive value of FOBT. We could not determine the sensitivity or negative predictive value of FOBT because patients with negative tests did not undergo colonoscopy.

Current CRC screening guidelines do not address whether warfarin should be discontinued before FOBT. Determining the effect of warfarin on FOBT sensitivity for colorectal neoplasia has important implications for CRC screening as some practitioners discontinue the use of warfarin before FOBT (10–12). On the basis of our retrospective study, the positive predictive value of the guaiac FOBT for significant colon pathology is not affected by the use of warfarin at the time of FOBT. These data support the practice of continuing warfarin before and during FOBT and avoiding any potential risk associated with the discontinuation of warfarin.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59:225–49. [PubMed: 19474385]
2. Espey DK, Wu XC, Swan J, et al. Annual Report to the Nation on the Status of Cancer, 1975–2004, Featuring Cancer in American Indians and Alaska Natives. Cancer. 2007; 110:2119–52. [PubMed: 17939129]
3. Pignone M, Rich M, Teutsch SM, et al. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventative Services Task Force. Ann Intern Med. 2002; 137:132–41. [PubMed: 12118972]
4. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993; 328:1365–71. [PubMed: 8474513]
5. Levin B, Lieberman DA, McFarland B, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin. 2008; 58:130–60. [PubMed: 18322143]
6. Smith RA, Cokkinides V, Eschenbach AC, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal and endometrial cancers. Cancer J Clin. 2002; 52:8–22.
7. Winawer SJ, Fletcher RH, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-update based on new evidence. Gastroenterology. 2003; 124:544–60. [PubMed: 12557158]
8. Allison JE. Review article: faecal occult blood testing for colorectal cancer. Aliment Pharmacol Ther. 1998; 12:1–10. [PubMed: 9692694]
9. Hemoccult Product Instructions. Beckman Coulter; Fullerton, CA: 1994.
10. Sharma VK, Vasudeva R, Howden CW. Colorectal cancer screening and surveillance practices by primary care physicians: results of a national survey. Am J Gastroenterol. 2000; 95:1551–6. [PubMed: 10894595]
11. Sharma VK, Corder FA, Fancher J, et al. Survey of the opinions, knowledge, and practices of gastroenterologists regarding colorectal cancer screening and use of the fecal occult blood test. Am J Gastroenterol. 2000; 95:3629–32. [PubMed: 11151904]
12. Sharma VK, Corder FA, Raufman JP, et al. Survey of the internal medicine residents' use of the fecal occult blood test and their understanding of colorectal cancer screening and surveillance. Am J Gastroenterol. 2000; 95:2068–73. [PubMed: 10950059]

13. Cios DA, Baker WL, Sander SD, et al. Evaluating the impact of study-level factors on warfarin control in U.S. based primary studies: a meta-analysis. Am J Health Sys Pharm. 2009; 66:916–25.
14. Levin MN, Raskob G, Landefeld S, et al. Hemorrhagic complications of anticoagulant treatment. Chest. 2001; 119(Suppl):108S–21S. [PubMed: 11157645]
15. Schappert SM, Nelson C. National Ambulatory Medical Care Survey:1995–96 summary. Vital Health Stat. 1999:i–vi. 1–122.
16. Lamb E. Top 200 prescription drugs of 2007. Pharm Times. May 1.2008 Issue 2008-05-8520.
17. Bini EJ, Rajapaksa RC, Weinshel EH. Positive predictive value of fecal occult blood testing in persons taking warfarin. Am J Gastroenterol. 2005; 100:1586–92. [PubMed: 15984986]
18. Lieberman DA, Holub JL, Moravec MD, et al. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic Black and White patients. JAMA. 2008; 300:1417–22. [PubMed: 18812532]
19. Levi Z, Rozen P, Hazazi R, et al. Sensitivity, but not specificity, of a quantitative immunochemical fecal occult blood test for neoplasia is slightly increased by the use of low-dose aspirin, NSAIDs, and anticoagulants. Am J Gastroenterol. 2009; 104:933–8. [PubMed: 19293792]
20. Pengo V, Pegoraro C, Cucchini U, et al. Worldwide management of oral anticoagulant therapy: the ISAM study. J Thromb Thrombolysis. 2006; 21:73–7. [PubMed: 16475046]
21. Ansell J, Hirsh J, Poller L, et al. Th e pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004; 126(Suppl 3):204S–33S. [PubMed: 15383473]
22. Gerson LB, Triadafilopoulos G, Gage BF. The management of anticoagulants in the periendoscopic period for patients with atrial fibrillation: a decision analysis. Am J Med. 2004; 116:451–9. [PubMed: 15047034]
23. Coon WW, Willis PW. Hemorrhagic complications of anticoagulant therapy. Arch Intern Med. 1974; 133:386–92. [PubMed: 4544112]
24. Wilcox CM, Truss CD. Gastrointestinal bleeding in patients receivinglong-term anticoagulant therapy. Am J Med. 1988; 84:683–90. [PubMed: 3261126]
25. Tabibian N. Acute gastrointestinal bleeding in anticoagulated patients: a prospective evaluation. Am J Gastroenterol. 1989; 84:10–2. [PubMed: 2783528]
26. Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal hemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. Gut. 1994; 35:464–6. [PubMed: 8174982]
27. Choudari CP, Palmer KR. Acute gastrointestinal hemorrhage in patients treated with anticoagulant drugs. Gut. 1995; 36:483–4. [PubMed: 7737549]
28. Younossi ZM, Strum WB, Schatz RA, et al. Eff ect of combined anticoagulation and low-dose aspirin treatment on upper gastrointestinal bleeding. Dig Dis Sci. 1997; 42:79–82. [PubMed: 9009119]
29. Greenberg PD, Cello JP, Rockey DC. Asymptomatic chronic gastrointestinal blood loss in patients taking aspirin or warfarin for cardiovascular disease. Am J Med. 1996; 100:598–604. [PubMed: 8678078]
30. Prichard PJ, Kitchingman GK, Walt RP, et al. Human gastric mucosal bleeding induced by low dose aspirin, but not warfarin. BMJ. 1989; 298:493–6. [PubMed: 2495079]
31. Blackshear JL, Baker VS, Holland A, et al. Fecal hemoglobin excretion in elderly patients with atrial fibrillation: combined aspirin and low-dose warfarin vs. conventional warfarin therapy. Arch Intern Med. 1996; 156:658–60. [PubMed: 8629878]
32. Fennerty MB, Davidson J, Emerson SS, et al. Are endoscopic measurements of colonic polyps reliable? Am J Gastroenterol. 1992; 88:496–500. [PubMed: 8470627]
33. Schoen RE, Gerber LD, Margulies C. The pathologic measurement of polyps size is preferable to the endoscopic estimate. Gastrointest Endosc. 1997; 46:492–6. [PubMed: 9434214]

Table 1

Patient characteristics according to warfarin status

Characteristic	No warfarin (*n*= 9,265) *n* (% of total)	Warfarin (*n*= 372) *n* (% of total)	*P* value warfarin vs. no warfarin	Missing (*n*= 629) *n* (% of total)
Gender				
Female	3,226 (35)	63(17)	<0.0001	197(31.3)
Male	6,039 (65)	309(83)		432(68.7)
Age (years)				
<50	1,180 (13)	4(1)	<0.0001	59(9.4)
50–59	3,441 (37)	72(19)		220 (35)
60–69	2,573 (28)	103(28)		180(28.6)
70–79	1,557 (17)	127(34)		132 (21)
80	514 (6)	66(18)		38 (6)
Race/ethnicity				
White non-Hispanic	7,382 (80)	329(88)	0.01	515(81.9)
Black non-Hispanic	548 (6)	12(3)		58(9.2)
Asian/Pacifi c Islander non-Hispanic	254 (3)	6(2)		6 (1)
Hispanic	977 (11)	21(6)		39(6.2)
Native American non-Hispanic	75 (<1)	3 (<1)		4 (<1)
Multiracial non-Hispanic	9 (<1)	0(0)		1 (<1)
Unknown	20 (<1)	1 (<1)		6 (1)
Site type				
Community/HMO	4,999 (54)	150(40)	<0.0001	439(69.8)
Academic	1,188 (13)	25(7)		22(3.5)
VA/military	3,078 (33)	197(53)		168(26.7)

VA, Veterans Affairs; HMO, Health Maintenance Organization.

Table 2

Prevalence of findings on colonoscopy according to warfarin status

	No	Yes	*P* value warfarin vs. no warfarin	Missing
Total	9,265	372		629
Signifi cant fi ndings				
Polyp >9mm	950 (10.3)	55(14.8)	0.003	81 (12.9)
Suspected malignant tumor	131 (1.4)	7(1.9)	0.48	12 (1.9)
Polyp >9mm or tumor	1,054 (11.4)	60(16.1)	0.001	93 (14.8)