Antithrombotics During Fecal Occult Blood Testing: A Meta-Analysis And Systematic Review

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Citation

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Abstract

Background: Fecal occult blood testing (FOBT) is commonly utilized as a screening modality for colon cancer. However, the effect of concurrent use of antithrombotics, including anticoagulation agents (warfarin, enoxaparin) and antiplatelet agents (aspirin, clopidogrel, NSAIDs, COX-2 inhibitors), on the yield of FOBT has not been well established. Therefore, a meta-analysis was performed to evaluate the effect of antithrombotics on the yield of FOBT.

Methods: Multiple databases were searched (July 2012). Studies examining the use of antithrombotics (aspirin, clopidogrel, NSAIDs, COX-2 inhibitors, warfarin, enoxaparin) versus no antithrombotics in patients with positive FOBT were included. Meta-analysis for the effect of antithrombotics or no antithrombotics for FOBT was performed by calculating pooled estimates of colonoscopy findings and detection of neoplasia, any adenoma, advanced adenoma, or colon cancer by odds ratio (OR) with fixed and random effects model. RevMan 5.1 was utilized for statistical analysis.

Results: Eight studies (N=2,800) met the inclusion criteria. No statistically significant differences were noted between FOBT with or without antithrombotics for colon cancer (OR 0.87; 95% CI: 0.69-1.11, p=0.26), advanced adenoma (OR 0.92; 95% CI: 0.62-1.37, p=0.70), colonoscopy findings (OR 0.76; 95% CI: 0.42-1.37, p=0.37), neoplasia (OR 0.87; 95% CI: 0.65-1.18, p=0.38), or any adenoma (OR 0.89; 95% CI: 0.67-1.20, p=0.45).

Conclusion: Among patients with positive FOBT, findings on colonoscopy do not appear to be affected by whether or not patients are taking antithrombotics.

Abbreviations: FOBT, fecal occult blood test; CRC, colorectal cancer; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval.

INTRODUCTION

Colorectal cancer (CRC) continues to be one of the leading causes of cancer-related mortality in the western world.1 Amongst the various modalities used for its screening, fecal occult blood test (FOBT) is widely used and has shown to decrease the incidence of colon cancer significantly in randomized controlled trials.2-6 However, certain medications have been hypothesized to affect FOBT, such as antiplatelet and anticoagulants.

Aspirin has been used in low doses for primary and secondary prevention of cardiovascular disease and is associated with significant gastrointestinal bleeding.7-9 The data on the use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) during fecal occult blood testing is limited and inconsistent.10-14 A joint guideline from the American Cancer Society, U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology recommends holding aspirin and other NSAIDs prior to stool collection for FOBT; however, guidelines from American Society of Gastrointestinal Endoscopy do not address this issue.15,16 Given the conflicting results in the literature regarding the yield of FOBT in patients on antithrombotics (aspirin, NSAIDs, clopidogrel, and enoxaparin), a meta-analysis was performed to evaluate the evidence further.

METHODS

Data Collection:

A three-stage process was used in the data collection. A comprehensive search was performed initially in MEDLINE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, CINAHL, and PubMed till July

2012. References of the retrieved articles and reviews were manually searched in the next step for any additional articles. Lastly, a manual search of abstracts submitted to the major conferences including Digestive Disease Week (DDW) and the American College of Gastroenterology (ACG) national meetings was performed from 2003-2012. All articles were searched irrespective of language, publication status (articles or abstracts), or results with the keywords being “fecal occult blood test”, “colorectal cancer screening”, “aspirin”, “clopidogrel”, and “warfarin.”

Selection Criteria:

Three authors (IA, SRP, and MLB) screened all of the articles and abstracts independently with resolution of any disagreements in the data by a third party (AC). Articles were selected if they compared the findings on colonoscopies after positive FOBT among adult patients who were on antithrombotics (aspirin, NSAIDS, clopidogrel, or enoxaparin) or controls (none of the above). Authors were contacted if data was incomplete or required clarification. Exclusion criteria included studies which did not compare antithrombotics to no antithrombotics populations.

Statistical Analysis:

A meta-analysis for the effect of antithrombotics or no antithrombotics for FOBT was performed by calculating pooled estimates of colonoscopy findings and detection of neoplasia, any adenoma, advanced adenoma, or colon cancer using odds ratio (OR) by fixed and random effects models. The meta-analysis was performed in accordance to the guidelines published for meta-analysis of observational studies in epidemiology.17 Heterogeneity among studies was assessed by calculating I^2 measure of inconsistency which was considered significant if $p < 0.10$ or $I2 > 50\%$. If heterogeneity was statistically significant, a study elimination analysis was utilized to examine for heterogeneity when certain studies were excluded from the analysis. RevMan 5.1 was utilized for statistical analysis. Publication bias was assessed by funnel plots.

Study Quality Assessment:

Study quality was assessed by using the Newcastle-Ottawa quality assessment scale for cohort studies which is based upon giving a star (★) for each of three quality parameters (selection, comparability, and outcome).18 Stars may range from zero stars (very poor quality cohort study) to nine stars (very strong quality cohort study).18 Studies with 7 stars or greater are considered as high quality studies.

RESULTS

Literature Search:

A total of 1,536 articles and abstracts were identified through the electronic database search. Figure 1 Of the 1,536 citations identified, we excluded 1,525 after screening the titles and abstracts. Of the remaining, eleven articles were examined by full-text review. Of these eleven articles, one article was excluded because it was an editorial and two more articles were excluded because outcome data was not reported separately. We included eight published articles in our current meta-analysis.19-25

Study Characteristics:

Of the eight included trials (n=2,800), four were prospective cohort studies19,20,24,26 and the other four were retrospective cohort studies.21-23,25 Table 1 The studies were performed at various locations in the United States, United Kingdom, Israel, and Italy between 1987 and 2010. All the studies included patients with a positive FOBT with subsequent colonoscopy. The quality of the studies was adequate as assessed by the Newcastle-Ottawa quality assessment scale and ranged from 7 to 9. Table 1

Analysis:

Primary outcomes of our meta-analysis included colon cancer and advanced adenoma. Secondary outcomes were colonoscopy findings, neoplasia, and any adenoma. No statistically significant differences were noted between FOBT with or without antithrombotics for colon cancer (OR 0.87; 95% CI: 0.69-1.11, p=0.26) or advanced adenoma (OR 0.92; 95% CI: 0.62-1.37, p=0.70). Figures 2 and 3 Similarly, no statistically significant differences were noted for secondary outcomes of colonoscopy findings (OR 0.76; 95% CI: 0.42-1.37, p=0.37) and detection of neoplasia (OR 0.87; 95% CI: 0.65-1.18, p=0.38) or any adenoma (OR 0.89; 95% CI: 0.67-1.20, p=0.45). Table 2 No publication bias was noted. Figure 4 Statistically significant heterogeneity was noted for four outcomes (colonoscopy findings, any adenoma, neoplasia and advanced adenoma) for which random effects model was used with no difference in results.

Figure 1

Selection of studies for inclusion in the meta-analysis of antithrombotics during fecal occult blood testing.

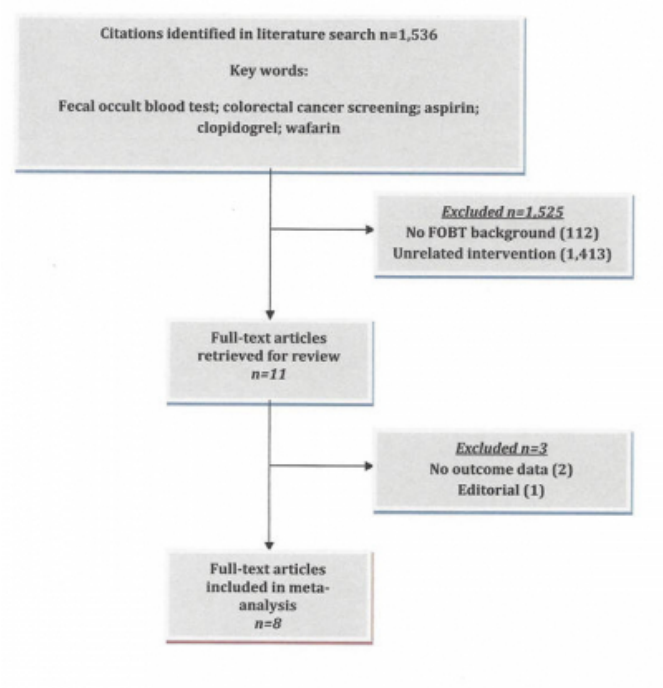


Figure 2

Forest plot showing no statistically significant effect on colorectal cancer detection for FOBT obtained with antithrombotics versus without antithrombotics.

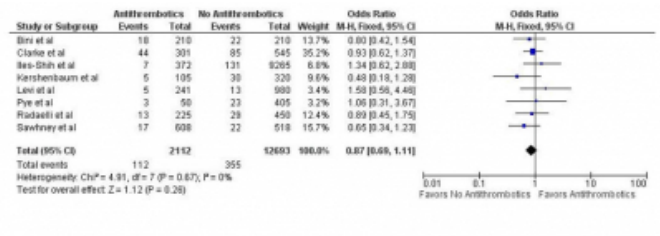


Figure 3

Forest plot showing no statistically significant effect on advanced adenoma detection for FOBT obtained with antithrombotics versus without antithrombotics.

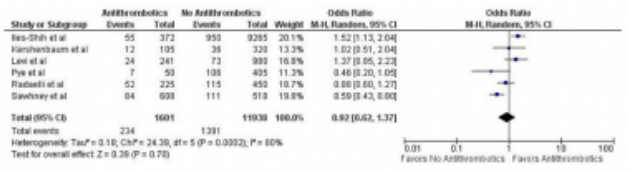


Table 1

Characteristics of studies included in meta-analysis.

Study	Design	Blinded	Location	FOBT	Patients (n)	Study Quality (No. stars)*
Pye et al – 1987	Cohort	No	UK	Hemoccult or Fecal EIA	455	7
Bini et al – 2005	Cohort	No	US	Hemoccult II	420	9
Clarke et al – 2006	Cohort	No	UK	Hema-screen	846	7
Levi et al – 2009	Cohort	No	Israel	i-FOBT	1221	9
Iles-Shih et al – 2010	Cohort	No	US	Hemoccult II	9637	9
Kershenbaum et al – 2010	Cohort	No	Israel	Hemoccult Sensa	425	8
Mandelli et al – 2010	Cohort	No	Italy	i-FOBT	516	9
Sawhney et al – 2010	Cohort	No	US	Hemoccult II or equivalent	1126	8

*Stars based upon Newcastle-Ottawa Scale for assessing the quality of cohort studies (0 stars = poor, 9 stars = excellent).[10]

Table 2

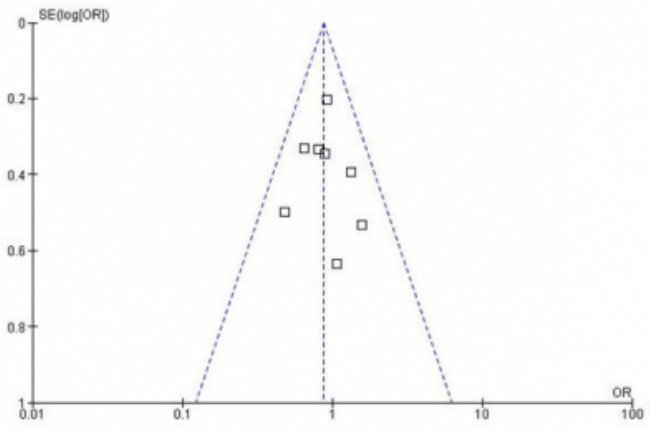
Summary of the analyses for FOBT obtained with antithrombotics versus without antithrombotics for colonoscopy findings and detection of neoplasia or any adenoma.

Outcome	Odds Ratio	95% Confidence Interval	p-Value	I^2
Colonoscopic Findings	0.76	0.42 – 1.37	0.37	91%*
Neoplasia	0.87	0.65 – 1.18	0.38	81%*
Any Adenoma	0.89	0.67 – 1.20	0.45	52%*

* Random effects model and an elimination analysis was performed given statistically significant heterogeneity.

Figure 4

Measure of publication bias using a funnel plot.



DISCUSSION

Colorectal cancer continues to be a significant cause of cancer related deaths in the United States. Amongst the various modalities used for its screening, FOBT is widely used and has shown to decrease its incidence. Aspirin use is common in the age group in which CRC screening becomes necessary.27 The reliability of FOBT in the setting of anticoagulation has been questioned as literature suggests that concomitant antithrombotic use can lead to false positive FOBT results. CRC cancer screening guidelines from major societies have conflicting opinions on this issue. Our meta-analysis was an effort to explore the evidence further.

Kahi et al considered use of aspirin and NSAIDs not a risk factor for a false positive FOBT in a prospective cohort study and recommended not to discontinue these medications at the time of FOBT.28 Their study was not included in our meta-analysis given that detailed colonoscopy findings were not reported for the two groups separately. Similarly, Mandelli et al found that positive predictive value of FOBT is not affected with the use of chronic low dose aspirin but their study had lower number of patients in the anticoagulants group leading to a possibility of type 2 error.29 Levi et al demonstrated that sensitivity of FOBT rather may be increased with the use of anticoagulants.30

Despite the results of above studies which suggest not stopping antithrombotics for FOBT, other studies have shown conflicting results. CRC screening with FOBT was not considered appropriate in patients on anticoagulation by Kewenter et al owing to its low sensitivity and positive predictive value in this setting.31 Similarly, Clarke et al in a prospective study favored stopping antithrombotics for FOBT because of increased likelihood of a negative colonoscopy in this setting; however, their results included warfarin with other antithrombotics.32 However, Ashraf et al in a recent meta-analysis on the use of warfarin during FOBT did not find any significant difference of the yield of FOBT during warfarin use.33 Similarly, Sawhney et al concluded that use of anticoagulants was associated with a lower the positive predictive value of FOBT for advanced colonic lesions and recommended stopping these medications if clinically feasible.34 Based on these conflicting results in the literature on the yield of FOBT in patients on antithrombotics, we conducted this meta-analysis to explore the evidence further.

In our current meta-analysis, we found that findings on colonoscopy do not appear to be affected by whether or not patients are taking antithrombotics as there were no statistically significant differences between FOBT results for patients on antithrombotics versus no antithrombotics for findings on colonoscopy and detection of neoplasia, including any adenoma, advanced adenoma, or colon cancer. Our meta-analysis has numerous strengths. First, a thorough and comprehensive literature search was performed with an extensive three stage search technique to maximize article recognition. Second, this meta-analysis was performed in accordance to the guidelines published for meta-analysis of observational studies in epidemiology.17 Third, all studies evaluated the two primary outcomes (i.e. advanced adenomas and colon cancer). Fourth, high-quality positive and negative studies were used for this meta-analysis per Newcastle-Ottawa scale. Fifth, a large number of patients in various populations were examined. Sixth, no publication bias was identified. Last, but not the least, this represents the first meta-analysis to-date assessing the yield of FOBT in patients on this subject with the potential to alter everyday clinical practice, particularly in the primary care setting.

There are some limitations to our current meta-analysis. First, the study quality was not ideal as it included observational studies given no randomized controlled trials are available on the issue at the moment. We tried to overcome it by following MOOSE guidelines specifically designed for observational studies and using adequate quality studies which was assessed by using the Newcastle-Ottawa scale. Second, different FOBT mechanisms were used in various studies with Hemoccult II or Hemoccult Sensa FOBT being the most common. Immunochemical FOBT (i-FOBT) was used in studies performed by Mandelli and Levi. Given the fact that many different formulations of FOBT are available and used around the world and since the

focus of this meta-analysis was the effect of antithrombotics on FOBT, we analyzed the overall effect. Finally, significant heterogeneity was noted for four outcomes (colonoscopy findings, any adenoma, neoplasia and advanced adenoma) for which random effects model was used to minimize the effect. In addition, a study elimination analysis was performed showing no heterogeneity for each of the outcomes with similar results.

To conclude, antithrombotic use does not appear to affect the yield of FOBT. Based upon the results of our meta-analysis, the continuation of these medications for FOBT screening for colorectal cancer may be considered, especially for those with significant cardiovascular risk factors.

CONFLICT OF INTEREST STATEMENT

No conflict of interest is apparent for any authors

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