ENDOSCOPY

A Comparison of the Rate of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin

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OBJECTIVES: **Early reports suggested that the risk of gastrointestinal bleeding (GIB) was higher for patients on non-vitamin K antagonist oral anticoagulants (NOACs) than for those on warfarin. We compared the incidence of GIB in our patients on NOACs with those on warfarin.**

METHODS: **We used our VA pharmacy database to identify patients taking NOACs (dabigatran, rivaroxaban, and apixaban) or warfarin between January 2011 and June 2015, and used the VistA system to identify those who were hospitalized for GIB. We included only patients with clinically significant GIB, defined as documented GI blood loss with a hemoglobin drop ≥2 g/dl, hemodynamic instability, and/or need for endoscopic evaluation, angiography, or surgery.**

RESULTS: **We identified 803 patients on NOACs and 6,263 on warfarin. One hundred and fifty-eight patients on warfarin had GIB (2.5%), compared with only five patients (0.6%) on NOACs (odds ratio=4.13; 95% confidence interval: 1.69–10.09). Blood transfusion for GIB was significantly more common in patients on warfarin than on NOACs (64.6% vs. 20%, *P*=0.04). Within 90 days of GIB hospitalization, 12 patients (7.6%) in the warfarin group died, whereas there were no deaths in the NOAC group.**

CONCLUSIONS: **In our patients, the incidence of GIB for those on warfarin was more than four times that for those on NOACs. Blood transfusions for GIB were more common in warfarin patients, and no NOAC patients died of GIB. In contrast to early reports, our findings suggest that the risk of GIB and subsequent complications is considerably lower for patients on NOACs than for patients on warfarin.**

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INTRODUCTION

Since their approval in 2010, non-vitamin K antagonist oral anticoagulants (NOACs) have been increasingly used instead of warfarin for a number of indications including prevention of thromboembolism in nonvalvular atrial fibrillation (AF), treatment of pulmonary embolism (PE) and deep venous thrombosis (DVT), and prophylaxis against DVT in patients undergoing knee or hip replacement surgery (1). Dabigatran (a direct thrombin inhibitor), rivaroxaban (a direct factor Xa inhibitor), and apixaban (another direct factor Xa inhibitor) are among the most commonly prescribed NOACs. Unlike warfarin, the NOACs provide patients the convenience of fixed dosing with no requirement for laboratory monitoring. However, there has been concern regarding the risk of gastrointestinal bleeding (GIB) for patients treated with NOACs.

In three landmark trials of different NOACs that ultimately led to their approval by the FDA, each NOAC was directly compared with warfarin for the prevention of thromboembolic complications in patients with non-valvular AF, and all were found to be non-inferior to warfarin in this regard (2–4). There were, however, apparent differences in the rates of GIB associated with these new agents compared with warfarin. In the RE-LY trial, the rate of GIB

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with dabigatran was higher than that with warfarin (3% vs. 2%), particularly when dabigatran was used in higher dosage (150 mg twice daily), with concomitant administration of aspirin or clopidogrel, among patients older than 75 years, and with lower levels of creatinine clearance (2). In the ROCKET AF trial, patients treated with rivaroxaban also had a significantly higher rate of GIB than those treated with warfarin (3.2% vs. 2.2%) (4). In the ARISTOTLE trial, patients treated with apixaban had a lower rate of major GIB than those treated with warfarin, but the difference between groups was not statistically significant (1.2% vs. 1.3%) (3). A recent meta-analysis suggested that patients treated with NOACs, overall, have a higher risk of GIB than those who receive standard care (odds ratio (OR) 1.45) (5). This was found to be particularly evident with dabigatran and apixaban, and especially in patients treated for thrombosis (in the setting of acute coronary syndrome or DVT/PE).

With such contradictory data, further studies are needed to better define the risk of GIB for patients treated with NOACs. The aforementioned landmark trials and most subsequent meta-analyses did not include GI bleeding as the primary outcome of interest, and some did not distinguish GI bleeding as a separate outcome from all causes of bleeding. Several recent observational studies have had contradictory results, and have focused only on dabigatran or on dabigatran and rivaroxaban (6–8). The purpose of this study was to compare the incidence of GIB in patients taking NOACs (including dabigatran, rivaroxaban, and apixaban) with that in patients on warfarin therapy at our Veterans Affairs Healthcare Center.

METHODS

This study was approved by the Institutional Review Board at the Dallas VA Medical Center.

Identification of cases

We identified all patients in the Veteran Affairs North Texas Healthcare System taking dabigatran, rivaroxaban, apixaban, or warfarin between January 2011 and June 2015 using our local VA pharmacy database. We then cross-referenced these patients with all patients during the same study period who had ICD-9-CM (International Classification of Diseases, 9th revision clinical modification) diagnosis codes pertaining to GIB in the Veterans Health Information Systems and Technology Architecture (VistA) system to identify all in-patient visits for, or complicated by, GIB. All cases so identified were then adjudicated through manual review of the patients' individual electronic medical records on the Computerized Patient Record System.

Data collection

Basic demographic information, patient comorbidities, medications, laboratory data, endoscopic procedure findings, blood product transfusions, in-patient complications, and 90-day complications post hospitalization (cerebrovascular accident, deep vein thrombosis, PE, or death) were recorded through manual chart review. Clinically significant GIB was defined as overt or occult GI blood loss resulting in hospitalization and associated with a decline in hemoglobin by ≥2 g/dl, hemodynamic instability (systolic blood pressure <90 mm Hg or heart rate >100 beats per minute) within 24 h of presentation, and/or need for endoscopic evaluation, angiography, or surgery.

Table 1. Rates of gastrointestinal bleeding for patients taking warfarin as compared with the NOACs, dabigatran, rivaroxaban, or apixaban

	GI bleed rate
Warfarin	158/6,263 (2.5%)
All NOACs	5/803 (0.62%)
Dabigatran	1/165 (0.61%)
Rivaroxaban	2/383 (0.52%)
Apixaban	2/254 (0.79%)

GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulants.

Statistical analysis

Continuous parameters are reported as mean±s.d., and discrete parameters are reported as *n* and percent (%). Data were explored for departures from normality with the Shapiro–Wilk test. Group comparisons were made with independent-samples *t*-tests or Mann–Whitney U-tests, where appropriate, for continuous data and Pearson's χ^2 tests, or Fisher's exact tests, where appropriate, for categorical data. Rates of GIB and the secondary outcomes (blood transfusion, endoscopic evaluation, angiography, surgery, 2 g drop in hemoglobin, hemodynamic instability, 90-day mortality, CVA within 90 days, DVT within 90 days, PE within 90 days, and length of hospital stay) are presented as percent of the event per group with 95% Wald confidence intervals (CIs) with normal approximation. ORs with 95% CI were calculated for the study outcomes. The study α was set to 0.05. Analyses were performed with SPSS 22.0 (Armonk, New York, USA) for Windows.

RESULTS

We identified a total of 803 patients taking NOACs (165 taking dabigatran, 384 taking rivaroxaban, and 254 taking apixaban) and 6,263 patients taking warfarin during our study time period. Patients prescribed apixaban were treated with 5 mg two times a day, while patients taking rivaroxaban were treated with 20 mg per day and those taking dabigatran with 150 mg two times a day. Five unique patients (0.6%) taking NOACs had a clinically significant GIB, compared with 178 clinically significant GIB events in 158 unique patients (2.5%, OR=4.13, $P<0.0001$; 95% CI: 1.69–10.09) taking warfarin (**Table 1**).

Indications for anticoagulation

Overall, indications for use of either the NOACs or warfarin were similar between the patient groups. Most patients were prescribed anticoagulation for either AF or for a history of PE and/or

DVT. Among the five patients taking NOACs who experienced a clinically significant GIB, one was taking dabigatran for AF, two were taking rivaroxaban (one for AF and a history of PE with DVT, and one for a factor V Leiden deficiency and a history of PE), and two were taking apixaban (one for AF and one for atrial flutter and a history of DVT). For patients taking warfarin who experienced a clinically significant GIB, 81 (51.3%) were taking warfarin for AF/flutter alone, 29 (18.4%) for a history of PE and/or DVT alone, and 7 (4.4%) for the presence of a prosthetic heart valve alone; the remainder of the patients were taking warfarin for varying combinations of the aforementioned indications, presence of a left atrial or left ventricular thrombus, peripheral vascular disease, history of cerebrovascular accident, portal or splenic vein thrombosis, presence of a left ventricular assist device, carotid artery dissection, or a hypercoagulable disorder such as protein S deficiency, antiphospholipid syndrome, and lupus anticoagulant.

Comparison of baseline characteristics between groups

Age, race, sex, and concomitant comorbid disease were similar between users of NOACs and warfarin. Notably, history of prior GIB or peptic ulcer disease and concomitant use of antiplatelet agents and proton pump inhibitors did not differ significantly between the two groups (**Table 2**). Charlson comorbidity index scores were higher for patients in the warfarin group than for those in the NOAC group (suggesting more severe illness in the warfarin users), but this difference did not reach statistical significance. Moreover, for the patients with AF, there was no difference in HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) scores between the groups (3.22 vs. 3, warfarin vs. NOAC group, P=0.61). Notably, 76 (42.7%) of the GIB events in patients taking warfarin occurred in the setting of a supratherapeutic international normalized ratio, and the average international normalized ratio for the group at the time of GIB was 3.6 (international normalized ratio range 1–28.2).

Among the five patients taking NOACs who had a clinically significant GIB, the cause of the bleeding was angioectasias in 2, hemorrhoids in 2, and postpolypectomy bleeding in 1. For the 158 patients with a significant GIB in the warfarin group, 55 (34.8%) had an upper GI bleed, 42 (26.6%) had a lower GI bleed, and 7 (4.4%) had bleeding from the small bowel; in 36 patients (22.8%), the source of bleeding was not determined (**Table 3**).

Secondary outcomes

Blood product transfusion (with packed red blood cells, platelets, and/or fresh frozen plasma) was significantly more common in the patients with GIB on warfarin than in those on NOACs (64.6% vs. 20%, P=0.042) (**Table 4**). In the patients with GIB on warfarin, 4 (2.5%) underwent angiography, one of whom (0.6%) required subsequent surgery; 4 additional patients (2.2%) were treated with surgery alone. In contrast, no patient in the NOAC group with GIB underwent angiography or surgery. Additionally, patients taking warfarin remained hospitalized more than two times as long as those taking NOACs (mean 7.7 vs. 3.8 days, P=0.068). Within 90 days of hospitalization for GIB, 12 patients

Table 2. Baseline characteristics of the patients who experienced GIB while taking NOACs or warfarin

Clinically significant GIB events	NOAC users (*n*=5)	Warfarin users (*n*=158)	P *value*
Mean age (years)	70.6	69.8	0.77
Male sex	5 (100%)	155 (98.1%)	0.76
Race			0.87
White	4 (80%)	114 (72.1%)	
Black	1 (20%)	37 (23.4%)	
Hispanic	0	7 (4.4%)	
Mean body mass index	29.6	28.8	0.77
History of tobacco use	4 (80%)	125 (76.6%)	0.86
History of prior GIB	2 (40%)	33 (21%)	0.31
Mean Charlson comorbidity index	1.8	3.51	0.08
HAS-BLED score[a]	3.0	3.22	0.61
Indication for anticoagulation			
Atrial fibrillation/flutter	4 (80%)	104 (65.8%)	0.51
PE/DVT	2 (40%)	38 (24.1%)	0.07
Prosthetic valve	0	21 (13.3%)	0.38
Other	0	26 (16.5%)	0.15
Comorbidities			
Congestive heart failure	1 (20%)	77 (48.7%)	0.21
Hypertension	4 (80%)	137 (86.7%)	0.67
Atrial fibrillation/flutter	4 (80%)	104 (65.8%)	0.51
Diabetes	1 (20%)	72 (45.6%)	0.26
History of CVA and/or TIA	0	26 (16.5%)	0.32
Coronary artery disease	3 (60%)	75 (47.8%)	0.59
Chronic kidney disease	0	55 (34.8%)	0.11
Chronic obstructive pulmonary disease	2 (40%)	38 (24.1%)	0.42
History of PE/DVT	2 (40%)	38 (24.1%)	0.07
Peripheral vascular disease	2 (40%)	27 (17.1%)	0.19
Cirrhosis	0	9 (5.7%)	0.58
Peptic ulcer disease	1 (20%)	9 (5.7%)	0.19
Malignancy	1 (20%)	33 (20.9%)	0.96
Prosthetic valve	0	21 (13.3%)	0.38
Left atrial or left ventricular thrombus	1 (20%)	7 (4.4%)	0.67
Carotid artery dissection	0	1 (.63%)	0.86
Factor 5 Leiden deficiency	1 (20%)	0	—
Antiphospholipid syndrome	0	2 (1.3%)	0.80
Protein C/S deficiency	0	1 (.63%)	—
Lupus anticoagulant	0	1 (.63%)	—
Portal vein thrombus	0	1 (.63%)	—

Table 2 continued on following page

Table 2. Continued

Clinically significant GIB events	NOAC users (*n*=5)	Warfarin users (*n*=158)	P *value*
Concomitant medications			
ASA (all doses)	2 (40%)	75 (47.5%)	0.74
NSAID	0	13 (8.2%)	0.50
Thienopyridine	0	16 (10.1%)	0.45
Heparin	0	10 (6.3%)	0.56
Use of any concomitant anticoagulant or antiplatelet	2 (40%)	90 (57%)	0.65
PPI	3 (60%)	56 (35.4%)	0.26
H2 blocker	1 (20%)	15 (9.5%)	0.44

ASA, acetylsalicylic acid; CVA, cerebrovascular accident; DVT, deep venous thrombosis; GIB, gastrointestinal bleeding; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; PE, pulmonary embolism; PPI, proton pump inhibitor; TIA, transient ischemic attack.
[a]Only calculated for patients with atrial fibrillation.

Table 3. Sources of GIB

	NOAC users	Warfarin users
Upper GI source	1 (20%)	55 (34.8%)
Angioectasias	1	6
Peptic ulcer disease	0	17
Esophagitis	0	5
Gastritis	0	1
GAVE	0	1
Varices (gastric or esophageal)	0	1
Dieulafoy	0	1
Mallory Weiss tear	0	1
Portal hypertensive gastropathy	0	2
Other	0	20
Small bowel source	1 (20%)	7 (4.4%)
Angioectasias	1	4
Ulcers	0	2
Malignancy	0	1
Lower GI source	3 (60%)	42 (26.6%)
Hemorrhoids	2	5
Postpolypectomy bleed	1	1
Angioectasias	0	4
Malignancy	0	5
Diverticulosis	0	13
Ischemia	0	5
Ileitis/anastomotic inflammation	0	2
Colon ulcers	0	6
Proctitis	0	1
Unknown source	2 (40%)	36 (22.8%)

GAVE, gastric antral vascular ectasia; GIB, gastrointestinal bleeding; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug.

(7.6%) in the warfarin group died and 2 (1.3%) experienced a DVT. None of the five patients in the NOAC group experienced death, CVA, or PE/DVT within 90 days of their hospitalization for GIB.

Subgroup analyses were conducted to focus only on those warfarin users who had AF/flutter or PE/DVT as an indication for use. This subgroup was statistically compared with the NOAC users. CVA, DVT, and PE within 90 days could not be analyzed due to low/no occurrences. The groups did not significantly differ on death within 90 days (P=0.55). The difference between the groups on the number of days hospitalized approached significance (P=0.08) with warfarin users trending toward longer stays (7.6 vs. 3.8 days). The need for transfusion also occurred at a higher rate among the subgroup of warfarin users (64% vs. 20%, P=0.046). No other significant differences emerged.

DISCUSSION

In this observational, "real-world" study of 803 patients on NOACs and 6,263 on warfarin for a variety of indications, the risk of clinically important GIB over a period of up to 54 months was more than fourfold higher in the warfarin users (2.5% vs. 0.6%, OR=4.13; 95% CI: 1.69–10.09). Furthermore, warfarin users with GIB had a higher rate of blood product transfusion (64.6% vs. 20%, P=0.042), and their length of hospitalization for GIB was more than two times that of the NOAC users (mean 7.7 vs. 3.8 days, P=0.068). Within 90 days of hospitalization for GIB, 12 patients (7.6%) in the warfarin group died, while there were no deaths among the five patients who had GIB on NOACs. These findings suggest that the risk of GIB and subsequent complications is less with the use of NOACs than with warfarin. A number of earlier reports on the risk of GIB with NOACs have described contradictory findings, and all published studies on this issue have had substantial limitations. To our knowledge, our study represents the largest single-center, observational study comparing GIB risk in NOAC users of dabigatran, rivaroxaban, and apixaban and warfarin users performed to date.

In the original landmark trials that led to FDA approval of the NOACs, dabigatran and rivaroxaban both were associated with a higher rate of GIB than warfarin, whereas apixaban had a lower rate (2–4). Since these publications, a number of studies have explored the issue of GIB with NOACs in a variety of *post hoc* analyses and meta-analyses of these data with the overall conclusion that NOACs likely portend a higher risk of GIB as compared with warfarin (5,9–12). One meta-analysis concluded that the risk of GIB was related to the use of higher doses of the NOACs, particularly dabigatran and edoxaban (13). However, it must be kept in mind that these studies were not originally designed to assess the outcome of GIB, as their intent was to assess the efficacy

Table 4. Secondary outcomes

	NOAC users	Warfarin users	P *value*	95% CI
Need for transfusion	1 (20%)	102 (64.6%)	0.042	−87.5 to −1.6%
Need for endoscopic evaluation	3 (60%)	140 (88.6%)	0.055	−57.9– to 0.7%
Need for angiography	0	4 (2.5%)	0.719	−16.5 to 11.4%
Need for surgery	0	4 (2.5%)	0.719	−16.5 to 11.4%
2 g Hb drop	4 (80%)	80 (50.6%)	0.196	−15.5 to 74.2%
Hemodynamic instability	2	24 (15.2%)	0.136	−8.0% to 57.6%
90-day mortality	0	12 (7.6%)	0.522	−31.1% to 15.9%
CVA within 90 days	0	0	—	—
DVT within 90 days	0	2 (1.3%)	0.80	−11.2 to 8.7%
PE within 90 days	0	0	—	—
Days in the hospital	$\bar{X}$=3.8, s.d.=1.3	$\bar{X}$=7.7, s.d.=7.6	0.068	−10.6 to 2.8

CI, confidence interval; CVA, cerebrovascular accident; DVT, deep venous thrombosis; Hb, hemoglobin; NOAC, non-vitamin K antagonist oral anticoagulant; PE, pulmonary embolism.

of these drugs to reduce the incidence of stroke. Consequently, there was no standard definition of GIB used across these studies, limiting interpretation of the data. Moreover, the use of warfarin in the clinical trial setting is likely superior to its use in daily practice with regard to the therapeutic monitoring and time in the therapeutic range. Last, patients enrolled in clinical trials are often not representative of real-world practice, as these groups often have strict inclusion and exclusion criteria, making it difficult to extrapolate the data to all of our patients.

To try and better assess the true risk of GIB in patients treated with NOACs as compared with warfarin, a number of postapproval observational studies have been performed using various administrative data sets. The benefit of these types of studies is that large number of patients can often be included; however, the data rely on the accuracy of administrative coding for diagnoses, and the primary outcome of GIB is not adjudicated with a chart review. Interestingly, several studies evaluated the risk of bleeding for dabigatran as compared with warfarin for patients with nonvalvular AF but have contradictory findings (7,8,14,15). In the United States, where dabigatran is approved only in a dose of 150 mg twice daily, two studies suggest that dabigatran has a higher risk for GIB compared with warfarin (8,15). However, in a retrospective cohort study in Denmark and another study in New Zealand (both where dabigatran is used in dosages of either 150 mg twice daily or 110 mg twice daily), neither found a difference in the rate of GIB for all dabigatran users compared with warfarin users, and one even found a significantly lower relative risk of GIB for patients taking the lower dose of dabigatran (hazard ratio 0.60; 95% CI: 0.37–0.93) (7,14). The notion that lower doses of dabigatran may confer a lower risk of GIB is supported by an analysis of pharmacokinetic data from the RE-LY trial (focusing specifically on plasma concentrations of dabigatran) that found the risk for major bleeding (including GIB) was directly related to dabigatran plasma trough levels (16).

A number of recent studies using US administrative data from a combination of commercially insured and Medicare/Medicaid patients have compared the risk of bleeding between rivaroxaban or dabigatran and warfarin, and found that risk to be not significant (6,17). Interestingly, however, when studies have looked specifically at older patients (>65 years of age) treated with these drugs, rates of GIB were significantly higher in those patients treated with dabigatran as compared with warfarin (hazard ratio 1.28; 95% CI: 1.14–1.44) (18). Moreover, this risk was also associated with women over the age of 75 years and men over the age of 85 years. In another study by this same group, when dabigatran was compared with rivaroxaban in this same elderly Medicare cohort, the risk of GIB was higher with rivaroxaban as compared with dabigatran (hazard ratio 1.40; 95% CI: 1.23–1.59) (19). In our study, the mean age for patients who experienced GIB using warfarin was 69.8 and 70.6 for NOACs users; however, our population was almost exclusively male, which may contribute to the lower risk of GIB seen in our study.

Our study has a number of considerable strengths. It is the largest, single-center, "real-world" study comparing rates of GIB for patients taking the three NOACs (dabigatran, rivaroxaban, or apixaban) compared with patients taking warfarin. The two groups were well matched with regard to mean age, prior history of GIB, and concomitant use of proton pump inhibitors and antiplatelet agents. All GIB events identified by ICD-9 codes were adjudicated by manual chart review, a feature not performed in the above-discussed administrative studies. Our study also is unique in that we recorded GIB outcome data regarding rates of blood transfusion, length of hospitalization, and deaths within 90 days. In doing so, we identified that patients taking NOACs who experienced a GIB had significantly lower rates of transfusion (20% vs. 69%, P=0.04) and spent approximately one-half of the number of days hospitalized compared with patients taking warfarin, which was a result that neared statistical significance (3.8 vs. 7.6 days, P=0.068).

Our study also has a number of limitations. The study is retrospective and therefore subject to the inherent biases of a retrospective study. Moreover, we identified possible GIBs first by a review of ICD-9 codes, which might miss events that are not properly coded. Subgroup analyses were limited by the small number of clinically significant GIBs that we observed in patients on NOACs (only 5 GIBs in 803 patients on NOACs). Furthermore, dabigatran, the NOAC most often associated with an increased risk of GIB in published reports, was the NOAC least used in our study population (20% of total NOAC users). Last, despite neither being statistically significant, the group on warfarin did have a higher burden of comorbid disease as well as a slightly higher rate of concomitant anticoagulant or antiplatelet use. It is possible that

either of these may have impacted the rates of GI bleeding in this group, as a higher burden of comorbid disease or the use of concomitant anticoagulant could increase the risk for bleeding.

In conclusion, our retrospective study found that the risk of GIB for patients on warfarin was more than four times that for patients on NOACs. Moreover, the patients who experienced GIB while taking warfarin required blood product transfusions more often and had longer hospital stays than those who bled while taking NOACs. None of the NOAC patients with GIB required angiography or surgery, and none died within 90 days of the hospitalization. These findings should allay the concerns of early reports suggesting that the risk of GIB with NOACs is higher than that with warfarin. Indeed, our study suggests that the risk of GIB and subsequent complications is considerably lower for patients on NOACs than for patients on warfarin. Future studies should focus on a comparison between these three NOACs, in addition to the recently approved edoxaban, given their differing pharmacokinetics, dosing, and mechanisms of action to assess safety between these agents.

CONFLICT OF INTEREST

Guarantor of the article: Linda A. Feagins, MD.

Specific author contributions: David J. Cangemi, MD—study design, data collection and analysis, interpretation of the data, and drafting of the manuscript; this author has approved final draft submitted. Timothy Krill, MD—data collection; this author has approved final draft submitted. Rick Weideman, PharmD—data collection and analysis, interpretation of the data, and critical review of the article for important intellectual content; this author has approved final draft submitted. Daisha J. Cipher, PhD—data analysis and statistics; this author has approved final draft submitted. Stuart J. Spechler, MD—interpretation of the data, critical review of the article for important intellectual content; this author has approved final draft submitted. Linda A. Feagins, MD—conception and design, data collection, analysis and interpretation of the data, critical revision of article for important intellectual content, and responsible for final approval of article.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Use of non-vitamin K antagonist oral anticoagulants (NOACs) is increasing as an alternative to warfarin.
- ✓ Concern has been raised that NOACs are associated with higher rates of gastrointestinal bleeding (GIB) as compared with warfarin, but these data have largely come from studies without GI bleeding as the primary focus.

WHAT IS NEW HERE

- ✓ In a veteran population, we found that low overall rates of GI bleeding in patients taking NOACs (0.6%).
- ✓ Patients treated with warfarin had nearly a five times higher risk for GI bleeding than those taking NOACs.

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