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Gastrointestinal Bleeding on Anticoagulant Therapy: Comparison of Patients Receiving Vitamin K Antagonists and Non-Vitamin K Oral Antagonists

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Abstract:

Objectives: Prior studies comparing gastrointestinal (GI) bleeding in patients receiving vitamin-K antagonists (VKA) and non-vitamin K antagonist oral anticoagulants (NOAC) focused on the crude rate of GI bleeding and less on severity of such events. The aim of our study was to assess characteristics of GI bleeding in patients on VKA therapy versus NOAC therapy.

Methods: Retrospective data collected from patients hospitalized with GI bleeding at Hadassah University Medical Center between January 2010 and July 2017. Retrieved data included demographics, laboratory results, clinical outcomes, and details regarding the bleeding characteristics, evaluation, treatment and hospitalization. Patients divided into two groups – those receiving VKA and those receiving NOAC.

Results: 514 patients who presented with GI bleeding were included. 439 patients were on VKA treatment and 75 on NOAC treatment. Atrial fibrillation was the indication for anticoagulation in 64% of VKA patients and in 91% of NOAC patients. The mean HAS-BLED score was the same in VKA and NOAC patient groups. Major bleeding events were seen in 38.3% of VKA patients and 30.7% of NOAC patients and life-threatening bleeding was seen in 34.4% of VKA patients and 26.7% of NOAC ($p<0.05$). Packed red blood cell and fresh-frozen plasma transfusions were administered less in the NOAC patients as compared to the VKA patients. No statistically significant differences in length of hospitalization, re-bleeding, or mortality were seen between groups.

Conclusions: GI bleeding events on NOAC therapy are less severe and use fewer hospital resources as compared to those treated with VKA.

Keywords: gastrointestinal bleeding; vitamin K antagonist; non vitamin K antagonist

Introduction

As life expectancy increases, there will likely be an ever larger number of patients being treated with anticoagulants for various indications including cardiac valve replacement, atrial fibrillation, venous thromboembolic disease, and hypercoaguable states.[1] For many years, vitamin K antagonists (VKA), primarily Warfarin, was administered when oral anticoagulant use was indicated.[2] In the 2000s, additional classes of oral anticoagulants termed non-vitamin K antagonist oral anticoagulants (NOAC) were introduced including direct thrombin inhibitors, such as Dabigatran, and factor Xa inhibitors, such as Rivaroxaban and Apixaban.

The primary studies to evaluate NOACs included RE-LY, ROCKET-AF, and ARISTOTLE and showed that they were not inferior to Warfarin for many indications, and even had lower rates of cerebral hemorrhage when compared to Warfarin[3-6]. One potential downside to NOAC use is a concern for a higher risk for gastrointestinal (GI) bleeding. Studies based on the above studies showed a higher risk for GI bleeding with Dabigatran and Rivaroxaban when compared to Warfarin.[7, 8] Meta analyses have also shown a higher risk of GI bleeding in NOACs as a class when compared to Warfarin[6, 9]. The hypotheses regarding the potential higher risk of GI bleeding in NOACs is based on differences in bioavailability and absorption. The bioavailability of NOACs ranges from approximately 6% to 80% as opposed to Warfarin which has bioavailability of 100%. Additionally, unabsorbed NOACs are active while unabsorbed Warfarin is inactive.[10, 11] NOACs remaining in the GI tract may have an increased localized anticoagulant effect. Nonetheless, many studies show an equal or even lower rate of GI bleeding among those treated with NOACs as compared to Warfarin.[12-14]

A meta-analysis of 12 randomized controlled studies with 102,729 patients showed no association between NOAC or VKA treatment and rate of major GI bleeding.[12] An additional study showed no difference in GI bleeding rates between those treated with Dabigatran or Rivaroxaban and Warfarin in patients younger than 75 years old.[13] Moreover, a retrospective study based on prescription data from the USA showed a four times higher risk of GI bleeding in patients prescribed Warfarin as compared to Dabigatran, Rivaroxaban, and Apixaban.[14] Most research studies that have compared GI bleeding in patients treated with Warfarin and NOACs relate only to the number of GI bleeding events. However, the absolute number of GI bleeding events does not adequately reflect the severity of bleeding, need for reversal agents, location of bleeding, and use of endoscopic management. In addition, development of potential reversal agents for NOACs including Idarucizumab and Andexanet may change bleeding outcomes, but as of yet have not been in extensive use[15, 16]. Therefore, use of blood products and need for endoscopic or other intervention may be higher in NOAC- associated GI bleeding as compared to Warfarin.

The aim of our study was to assess the differences in characteristics of GI bleeding among patients treated with NOACs as compared to those treated with VKAs, including endoscopic findings, clinical characteristics, use of blood products, and re-bleeding rates.

Methods

Patients

The medical records of patients treated with oral anticoagulants and hospitalized due to GI bleeding at Hadassah University Medical Center between January 1, 2010 and July 31, 2017 retrospectively reviewed. Patients were included in the study if they were 18 years of age and older and hospitalized with ICD-9 codes 578 or 569.3, and were receiving treatment or had stopped treatment within three days with any of the following medications: Dabigatran, Rivaroxaban, Apixaban, Warfarin, or Acenocoumarol. Patients were excluded if they were recipients of a bone marrow transplant, terminal cancer patients, initially admitted with septic shock, trauma patients, electively hospitalized, admitted with bleeding from the mouth or nose, or were receiving treatment with two anticoagulant medications (such as those being bridged to Warfarin with Enoxaparin).

Bleeding definition

Gastrointestinal bleeding included patients with hematemesis, “coffee-ground” emesis, melena, and hematochezia. In addition, patients

characterized as having GI bleeding if they presented with secondary symptoms of GI bleeding or anemia, including syncope, chest pain, shortness of breath, or weakness, and those symptoms were later found to be secondary to GI bleeding based on objective clinical, laboratory, or endoscopic findings, including blood or "coffee-ground" appearance of fluid in a naso-gastric tube, acute anemia with positive fecal occult blood test, or endoscopic evidence of GI bleeding.

Definition of major bleeding and life-threatening bleeding was based on studies by Schulman et al. and the European Medicines Agency[17, 18] as follows:

Major bleeding: Decrease of 2 to 5 grams/deciliter of hemoglobin level or administration of two or three units of packed red blood cells (pRBC).

Life-threatening bleeding: Decrease of at least 5 grams/deciliter of hemoglobin level, administration of at least four units of pRBCs, need for inotropes, need for surgical intervention as treatment for GI bleeding, or mortality secondary to GI bleeding.

Data collection

Patient demographics that were collected included age, gender, anticoagulant medication use, indication for anticoagulant use, anti-platelet medication use, use of non-steroidal anti-inflammatory medication (NSAID), use of steroid medications, use of proton pump inhibitors (PPI), and use of H2 receptor blockers. Risk factors for GI bleeding were also collected, including: hypertension, diabetes, renal failure, liver failure, history of cerebrovascular event, use of alcohol or drugs, and a history of GI bleeding. Additional data collected included laboratory testing, interventions performed (blood product use, endoscopic interventions, and surgical interventions), length of hospitalization (as it related to GI bleeding), need for and length of intensive care unit (ICU) stay, and thirty-day mortality. The HAS-BLED score for each patient was calculated.[19]

Endoscopic data that was collected included location of GI bleeding (Upper: esophagus, stomach, and duodenum, Small intestines: jejunum and ileum, and Lower: colon and rectum), cause of GI bleeding (e.g. peptic ulcer disease, malignancy, vascular malformation), if active bleeding was present, and endoscopic interventions performed. Endoscopic data was used from the same hospitalization as that for admission for GI bleeding, but if endoscopic testing performed after discharge in the ambulatory setting then that data was used to determine the location and cause of bleeding.

Ethics approval

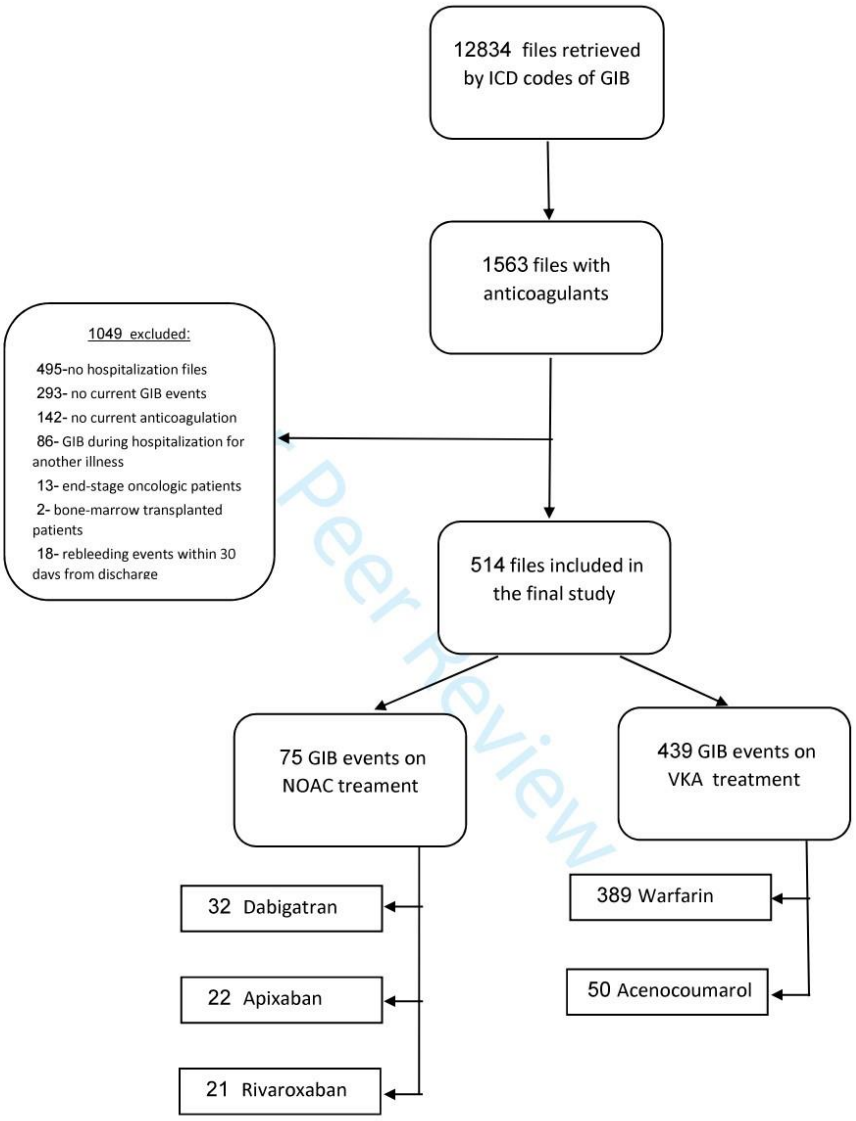
The study receive approbation by the Helsinki Committee of the Hadassah University Medical Center and consent waiver was obtained, as this was a retrospective study.

Statistics

Continuous variables were presented as average ± standard deviation, and the categorical variables were presented in percentages. Comparisons between groups regarding categorical parameters were presented in the form of Odds ratio and 95% confidence interval. Statistical significance between the groups was measured using the Student t-test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables. A p value< 0.05 was considered statistically significant. A univariate analysis was performed to determine the association of each clinical or demographic parameter on the risk for severe or life-threatening bleeding. Due to the lack of association of any of these parameters for severe or life-threatening bleeding, a multivariable/Cox regression analysis was not performed.

Results

Between January 1, 2007 and July 31, 2017 there were 12,834 patient records containing diagnosis codes for GI bleeding. Upon review of these records including medications, 1,563 of the GI bleeding events were associated with anticoagulant therapy. Of these, 1,049 did not meet the inclusion criteria (Figure 1).



ICD International Statistical Classification of Diseases and Related Health Problems 10th Revision, VKA Vitamin K antagonist, NOAC Non Vitamin-K Antagonist Oral Anti-Coagulant

Figure 1: Flowchart of the study population selection

There were 514 GI bleeding events in the setting of anticoagulant therapy of which 439 involved VKA and 75 involved NOAC.

Patient characteristics are detailed in Table 1.

TABLE 1: **Demographic and clinical parameters of study participants**

	VKA n=439	**NOAC n=75**	**p VALUE**
AGE *median [range]*	76 [24-99]	82 [43-98]	<0.05
<65 *(n)*	19% (83)	8% (6)	<0.05
≥65 *(n)*	81% (356)	92% (69)	
GENDER *(n)*			
M	55% (243)	56% (42)	0.92
F	45% (196)	44% (33)	
ANTICOAGULANT *(n)*			

Warfarin	89% (389)	-	
Acenocoumarol	11% (50)	-	
Apixaban	-	29% (22)	
Dabigatran	-	43% (32)	
Rivaroxaban	-	28% (21)	
INDICATION† *(n)*			
atrial fibrillation	64% (283)	91% (68)	<0.05
synthetic heart valve	24% (105)	1% (1)	<0.05
deep vein thrombosis / pulmonary embolism	13% (58)	8% (6)	0.21
Hypercoagulation state	4% (17)	7% (5)	0.34
arterial thrombosis	11% (48)	5% (4)	0.14
other‡ / unknown	3% (14)	0	0.24
RISK FACTORS† *(n)*			
diabetes mellitus	35% (154)	52% (39)	<0.05
arterial hypertension	25% (111)	8% (6)	<0.05
chronic kidney disease	32% (142)	37% (28)	0.40
chronic liver disease	6% (28)	3% (2)	0.29
past cerebral vascular injury	22% (97)	31% (23)	0.11
past gastrointestinal bleeding	32% (139)	25% (19)	0.27
labile INR	7% (31)	n/a	n/a
alcohol / drug abuse	2% (7)	1% (1)	1
OTHER MEDICINES† *(n)*			
NSAIDs / Aspirin	42% (185)	28% (21)	<0.05
Clopidogrel, Prasugrel, Ticagrelor	7% (30)	5% (4)	0.80
Corticosteroids	12% (51)	8% (6)	0.36
PPI / H_2-blocker	51% (226)	51% (38)	0.90
HAS-BLED SCORE *mean [±SD]*	3.01 [1.31±]	3.07 [1.12±]	0.73
0-2 *(n)*	36% (158)	33% (25)	0.66
≥3 *(n)*	64% (281)	67% (50)	

VKA Vitamin K antagonist, NOAC Non Vitamin-K Antagonist Oral Anti-Coagulant, INR International normalized ratio of prothrombin time, NSAIDS Nonsteroidal anti-inflammatory drugs, H_2 Histamine-2 receptor, PPI Proton-pump inhibitor, HAS-BLED Scoring assessment of major bleeding in patients with atrial fibrillation, SD Standard Deviation, N/A non-applicable

†Patients could be included in more than one category

‡ Including portal vein thrombosis, Budd-Chiari syndrome, Accidental Warfarin use

The median age of patients in the NOAC group was higher in comparison to the VKA group. Furthermore, there was a higher proportion of patients older than 65 years in the NOAC group (92% vs. 81% in the VKA group, p=0.021). The primary indication for anticoagulant treatment in the NOAC group was atrial fibrillation (91%) with a significantly lower percentage of patients in the VKA group that were taking anticoagulation for atrial fibrillation (64%, p<0.001). Concerning co-morbidities, a significantly higher proportion of patients in the NOAC group had diabetes (52% vs. 35%, p=0.005) while the proportion of patients with hypertension was higher in the VKA group (25% vs. 8%, p=0.001). Concomitant use with NSAIDs was higher in the VKA group (42% vs. 28%, p=0.021) and there was no significant difference in the use of PPIs or H2 blockers between the two groups.

The calculated HAS-BLED score was similar between the two groups: 3.01 (95% CI 2.89-3.13) for the VKA group and 3.07 (95% CI, 2.81-3.33) for the NOAC group (p = 0.73).

Clinical Presentation

The most common clinical presentation of GI bleeding in the NOAC group was melena (53.3%) while the most common clinical presentation in the VKA group was bright red blood per rectum (41.7%) (Table 2).

TABLE 2: **Clinical presentation and endoscopic therapies**

	VKA n=439	**NOAC n=75**	**p VALUE**	**ODDS RATIO [95% CI] NOAC vs VKA**
PRESENTATION *(n)*				
hematemesis / coffee ground vomiting	16.2% (71)	10.7% (8)	0.22	0.61 [0.29-1.34]
melena	38.5% (169)	53.3% (40)	<0.05	1.82 [1.11-2.99]
bright rectal bleeding	41.7% (183)	33.3% (25)	0.17	0.7 [0.42-1.17]
anemia with positive FOBT	3.6% (16)	2.7% (2)	1	0.72 [0.16-3.21]
INVESTIGATION† *(n)*				
gastroscopy	57.9% (254)	62.7% (47)	0.44	1.22 [0.73-2.02]
colonoscopy	38.7% (170)	40% (30)	0.83	1.05 [0.64-1.74]
enteroscopy	0.5% (2)	2.7% (2)	0.10	n/a
video-capsule	1.1% (5)	1.3% (1)	1	1.17 [0.14-10.18]
CTA/CTE	9.6% (42)	20% (15)	<0.05	2.36 [1.23-4.52]
angiography	2.1% (9)	2.7% (2)	0.67	1.3 [0.27-6.18]
not investigated	18.9% (83)	18.7% (14)	0.96	0.98 [0.52-1.85]
ACTIVE BLEEDING ON INVESTIGATION *(n)*	14.6% (64)	12% (9)	0.55	0.8 [0.38-1.68]
ENDOSCOPIC TREATMENT[1] *(n)*				
adrenaline injection	8.4% (37)	8% (6)	0.90	0.94 [0.38-2.32]
coagulation / argon	7.5% (33)	8% (6)	0.88	1.07 [0.43-2.65]
endoclip	5.9% (26)	9.3% (7)	0.30	1.64 [0.68-3.92]

banding	2.3% (10)	2.7% (2)	0.69	1.17 [0.25-5.47]
polypectomy	1.8% (8)	2.7% (2)	0.65	1.47 [0.31-7.09]
Total	18.7% (82)	20% (15)	0.79	1.09 [0.59-2.01]

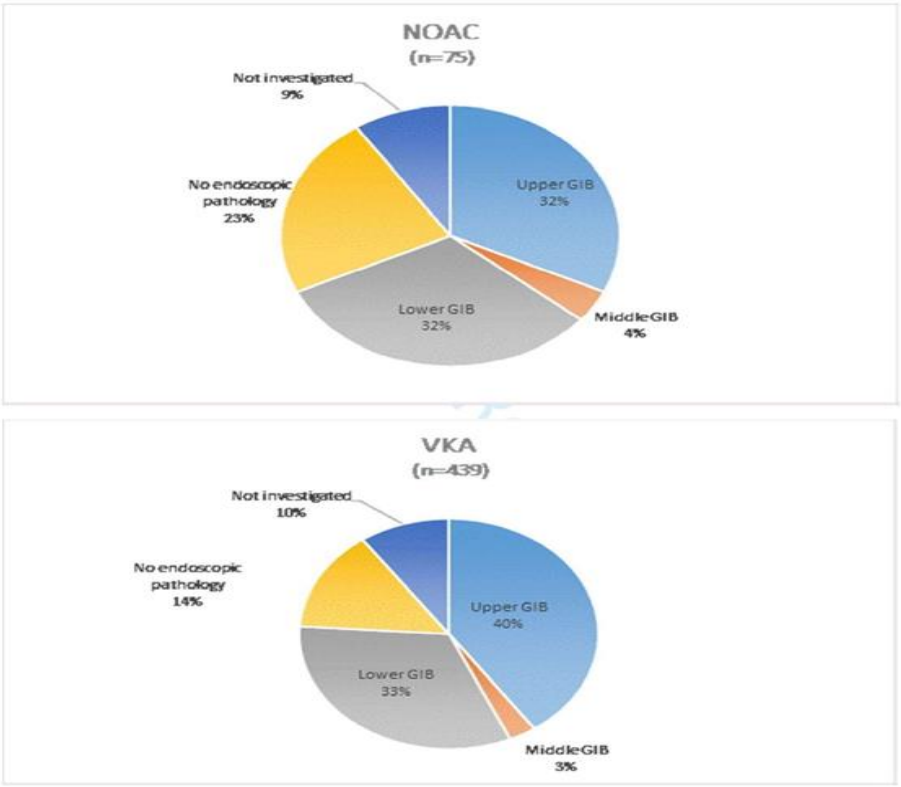
VKA Vitamin K antagonist, NOAC Non Vitamin-K Antagonist Oral Anti-Coagulant, FOBT Fecal occult blood test, CTE Computed tomography enterography, CTA Computed tomography angiography, CI Confidence interval, n/a non-applicable

[†]Patients could be included in more than one category

There was no significant difference in the proportion of patients who underwent upper endoscopy, colonoscopy, or angiography between the two groups. Approximately 19% (n=97) of patients in both groups did not undergo any of those tests as part of the bleeding evaluation. Of these, 42 (43.3%) patients had resolution of bleeding prior to investigation and no further intervention was pursued, 30 patients (30.9%) had prior testing, 14 patients (14.4%) refused or had health care agent refuse testing, 4 patients (4.1%) were found to have peri-anal disease as cause of bleeding, and 7 patients (7.2%) died prior to testing. Active bleeding at the time of endoscopic or angiographic procedure was seen in 12% of NOAC patients and 14.6% of VKA patients (p=0.55). Twenty percent of NOAC patients underwent therapeutic endoscopic interventions as compared to 18.7% of VKA patients (p=0.79).

Endoscopic findings

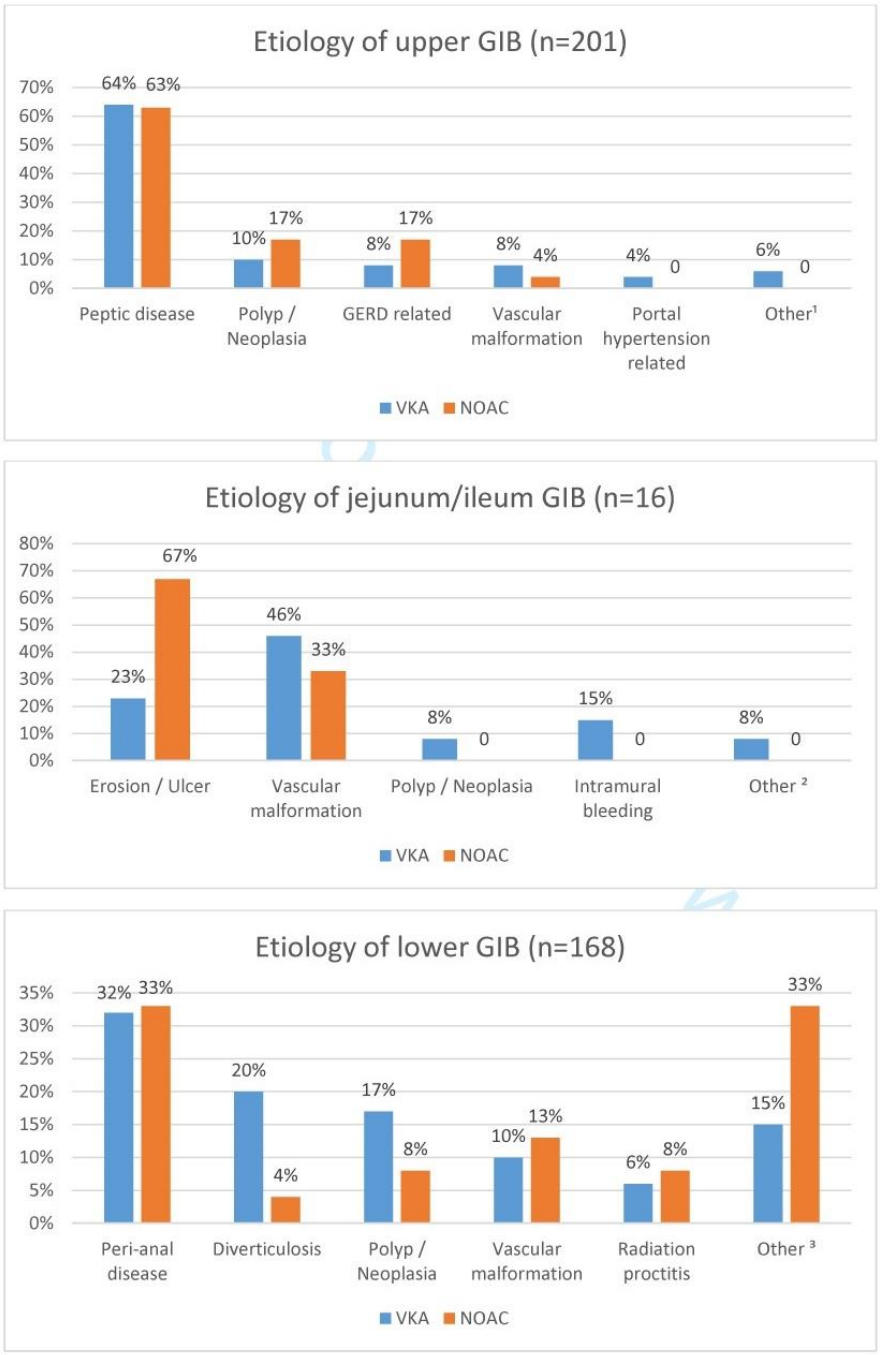
There was no significant difference between the groups concerning location of bleeding. Overall, 39.1% of patients had bleeding from the upper GI tract, 32.7% in the lower GI tract, and 3.1% in the jejunum/ileum. After review of post-discharge and ambulatory medical records, in 15.4% of patients who underwent an endoscopic intervention, the location of bleeding was not identified and 9.7% of patients did not undergo endoscopic evaluation (Figure 2).



VKA Vitamin K antagonist, NOAC Non Vitamin-K Antagonist Oral Anti-Coagulant, GIB Gastrointestinal bleeding

Figure 2: Comparison of sources for GI bleeding between VKA and NOAC

The most common etiology of upper GI bleeding events was peptic ulcer disease (64% in the VKA group, and 63% in the NOAC group, p=0.85). Additional etiologies of upper GI bleeding in the VKA and NOAC groups included bleeding neoplasms/polyps (10% and 17%, respectively), reflux esophagitis (8% and 17%, respectively), vascular malformations (8% and 4%, respectively) and other causes (Figure 3).



GERD Gastro-esophageal reflux disease, VKA Vitamin K antagonist, NOAC Non Vitamin-K Antagonist Oral Anti-Coagulant
†Mallory-Weiss tear, Aorto-duodenal fistula, post-polypectomy, bleeding from surgical anastomosis, gastric antral vascular ectasia
‡ Ischemia of the small bowel
§Colitis, post polypectomy, bleeding from surgical anastomosis, perforation, ileo-colonic fistula

Figure 3: Etiology of GI bleeding by location

Causes of small intestinal bleeding included erosions, ulcers, and vascular malformations and there were two patients in the VKA group who were found to have intestinal wall hematomas. One third of the patients with lower GI bleeding were found to have an anorectal source (hemorrhoids, fissure, or solitary rectal ulcer). Vascular malformations, including Dieulafoy lesions and angiodysplasias accounted for 10.1% of GI bleeding cases with no significant difference between NOAC and VKA patients.

Severity of GI bleeding

Among patients receiving NOACs the severity of bleeding was minor in 42.7% of cases as compared to 27.3% among patients receiving VKA (p=0.007) (Table 3).

TABLE 3: Clinical course of gastrointestinal bleeding

	VKA n=439	**NOAC n=75**	**p VALUE**	**ODDS RATIO [95% CI] NOAC vs VKA**
GIB SEVERITY *(n)*				
Minor bleeding	27.3% (120)	42.7% (32)		1.97 [1.2-3.27]
Major bleeding	38.3% (168)	30.7% (23)	<0.05	0.71 [0.42-1.21]
Life-threatening bleeding	34.4% (151)	26.7% (20)		0.69 [0.4-1.2]
LABORATORY *mean [±SD]*				
first hemoglobin (g/dL)	9.44 [±2.76]	9.37 [±2.9]	0.82	
lowest hemoglobin (g/dL)	8.32 [±2.21]	8.66 [±2.63]	0.24	
hemoglobin drop (g/dL)	1.13 [±1.43]	0.71 [±0.97]	<0.05	
first INR (IU) *median [±SD]*	3.12 [±3.56]	1.52 [±1.20]	n/a	
BLOOD PRODUCTS *mean [±SD]*				
packed red blood cells	2.97 [±4.57]	2.05 [±2.82]	0.09	
fresh frozen plasma	2.49 [±4.0]	1.37 [±6.28]	<0.05	
thrombocytes	0.95 [±7.22]	0.44 [±1.76]	0.54	
cryoprecipitate	0.3 [±2.43]	0.13 [±1.15]	0.57	
PCC *(n)*	1.1% (5)	1.3% (3)	1	
CLINICAL PARAMETERS *mean [±SD], (n)*				
hospital stay (days)	10.08 [±9.67]	8.75 [±6.03]	0.11	
ICU stay (days)	1.79 [±5.14]	0.85 [±3.25]	<0.05	
vasopressor use	5.2% (23)	2.7% (2)	0.56	0.50 [0.11-2.15]
re-bleeding (30 days)	12.5% (55)	10.7% (8)	0.65	0.83 [0.38-1.83]

re-endoscopy (30 days)	8.9% (39)	6.7% (5)	0.53	0.73 [0.28-1.92]
for re-evaluation	48.7% (19)	40% (2)	1	0.7 [0.11-4.74]
for bleeding stop	51.3% (20)	60% (3)	1	1.42 [0.21-9.49]
surgery for bleeding	1.8% (8)	0	0.61	n/a
mortality (30 days)	6.2% (27)	8% (6)	0.61	1.33 [0.53-3.33]
exsanguination	18.5% (5)	16.7% (1)	1	0.88 [0.08-9.29]
other complication	81.5% (22)	83.3% (5)	1	1.14 [0.11-11.99]

VKA Vitamin K antagonist, NOAC Non Vitamin-K Antagonist Oral Anti-Coagulant, INR International normalized ratio of prothrombin time, PCC Prothrombin complex concentrate, SD Standard Deviation, CI Confidence interval, n/a non-applicable

Major and life-threatening bleeding rates were 30.7 and 26.7% in NOAC patients and of 38.3 and 34.4% in VKA patients, respectively ($p<0.05$). Rates of severity of GI bleeding for each specific medication shown in Table 4.

Table 4: Comparison of severity of GI bleed by medications

	Rivaroxaban n=21	Dabigatran n=32	Apixaban n=22	Acenocoumarol n=50	Warfarin n=389
(n) **GIB SEVERITY**					
Minor bleeding	42.9% (9)	37.5% (12)	50% (11)	24% (12)	27.8% (108)
Major bleeding	42.9% (9)	25% (8)	27.3% (6)	40% (20)	38% (148)
Life-threatening bleeding	14.3% (3)	37.5% (12)	22.7% (5)	36% (18)	34.2% (133)

Secondary Endpoints

There was a statistically significant difference in the decrease in hemoglobin levels from admission to the lowest level during hospitalization: For NOAC patients there was a decline of 0.7 g/dL vs. a decline of 1.1 g/dL for VKA patients ($p=0.002$). There was no statistically significant difference in the mean amount of packed RBC transfusions between the two groups (2.1 units for NOAC vs. 3.0 units for VKA; $p=0.09$), but there was a significant difference in the mean amount of fresh frozen plasma units that were transfused (1.4 units for NOAC vs. 2.5 units for VKA; $p=0.042$). There was no difference in the use of other blood products. (Table 3).

Mean hospital length of stay was shorter for NOAC patients (8.8 days vs 10.1 days; $p=0.11$) but did not reach statistical significance. However, NOAC patients did, on average, spend a shorter time in the ICU (0.9 days vs 1.8 days; $p=0.039$). There was no significant difference in recurrent bleeding during hospitalization or within thirty days, which ranged from 10.7%-12.5% among the two groups. Repeat endoscopy was performed in 6.7% of NOAC patients and 8.9% of VKA patients. Surgical intervention was rare and was required in 8 patients, all within the VKA group (1.8%). There was mortality of 8% in the NOAC group and 6.2% in the VKA group ($p=0.61$), and uncontrolled bleeding was the cause of death in fewer than 20% of deaths in both groups.

When evaluating all patients with GI bleeding in this study, there was no significant difference in minor bleeding vs major/life-threatening bleeding with regards to age, gender, indication for anticoagulation, co-morbidities, concomitant medication use, or HAS-BLED score (Table 5).

TABLE 5: Univariate analysis for parameters predicting severity of GIB

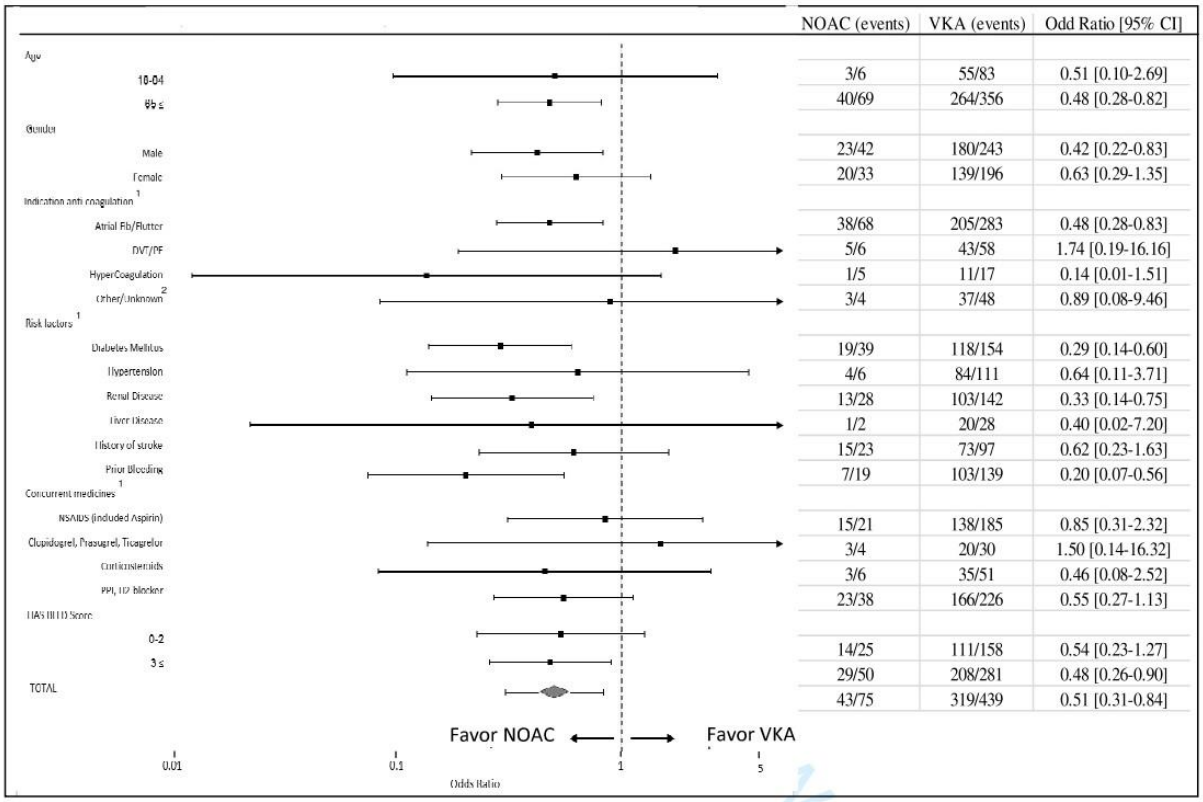
	minor bleeding	**life-threatening or major bleeding**	**p VALUE**
TOTAL *(n)*	29.6% (152)	70.4% (362)	
AGE *median [range]*	73.7 [±12.6]	74.8 [±12.1]	0.35
<65 *(n)*	34.8% (31)	65.2% (58)	0.23
≥65 *(n)*	28.5% (121)	71.5% (304)	
GENDER *(n)*			
m	28.8% (82)	71.2% (203)	0.66
f	30.6% (70)	69.4% (159)	
INDICATION† *(n)*			
atrial fibrillation	30.8% (108)	69.2% (243)	0.38
synthetic heart valve	24.5% (26)	75.5% (80)	0.20
deep vein thrombosis / pulmonary embolism	25% (16)	75% (48)	0.39
Hypercoagulation state	45.5% (12)	54.5% (12)	0.10
arterial thrombosis	23.1% (12)	76.9% (40)	0.28
other‡ / unknown	21.4% (3)	78.6% (11)	0.77
RISK FACTORS† *(n)*			
diabetes mellitus	29% (56)	71% (137)	0.83
arterial hypertension	24.8% (29)	75.2% (88)	0.20
chronic kidney disease	31.8% (54)	68.2% (116)	0.44
chronic liver disease	30% (9)	70% (21)	0.96
past cerebral vascular injury	26.7% (32)	73.3% (88)	0.43
past gastrointestinal bleeding	30.4% (48)	69.6% (110)	0.79
labile INR	25.8% (8)	74.2% (23)	0.64
alcohol / drug abuse	12.5% (1)	87.5% (7)	0.45
OTHER MEDICATIONS *(n)*			
NSAIDs / Aspirin	25.7% (53)	74.3% (153)	0.12
Clopidogrel, Prasugrel, Ticagrelor	23.4% (11)	67.6% (23)	0.71
Corticosteroids	33.3% (19)	66.7% (38)	0.51
PPI / H_2-blocker	28.4% (75)	71.6% (189)	0.55
HAS-BLED SCORE *(n)*			
0-2	31.7% (58)	68.3% (125)	0.43
≥3	28.4% (94)	71.6% (237)	

NR International normalized ratio of prothrombin time, NSAIDS Nonsteroidal anti-inflammatory drugs, H_2 Histamine-2 receptor, PPI Proton-pump inhibitor, HAS-BLED Scoring assessment of major bleeding in patients with atrial fibrillation, SD Standard Deviation

†Patients could be included in more than one category

‡ Including portal vein thrombosis, Budd-Chiari syndrome, Accidental Warfarin use

Figure 4 shows how these characteristics were associated with the risk for major/life-threatening bleeding in comparison between NOAC and VKA patients.



NOAC Non Vitamin-K Antagonist Oral Anti-Coagulant, VKA Vitamin K antagonist, CI Confidence interval, DVT Deep vein thrombosis, PE Pulmonary embolism, NSAIDS Nonsteroidal anti-inflammatory drugs, PPI Proton-pump inhibitor, H_2 Histamine-2 receptor, HAS-BLED Scoring assessment of major bleeding in patients with atrial fibrillation

†Patients could be included in more than one category

‡ Including portal vein thrombosis, Budd-Chiari syndrome, Accidental Warfarin use

Figure 4: Forrest plot depicting risk factors for major/life-threatening bleeding

Discussion

The results of this study show that patients treated with NOACs who present with GI bleeding have, on average, less severe bleeding events and require fewer blood products as compared to VKA patients. Other studies have shown that demographics, co-morbidities, and concomitant medications influence severity of GI bleeding events among those treated with oral anticoagulation[6, 10, 19, 20]. Our study results demonstrate that the type of anticoagulant medication directly influences the severity of GI bleeding.

A decreased risk for major/life-threatening bleeding was seen in all of the NOACs, but was least evident for Dabigatran. This may be due to the low bioavailability of Dabigatran, and a potential corrosive effect of tartaric acid within the medication.[10]

While we did find a lower need for blood products and shorter ICU stay in NOAC patients as compared to VKA patients this did not correspond to a lower mortality rate. This is in contrast to a study that included all bleeding events and not just GI bleeding, which did show a difference in mortality.[21] Additionally, Majeed et al. found a higher need for packed RBCs in GI bleed patients receiving Dabigatran as compared to patients receiving Warfarin, while at the same time patients receiving Dabigatran had shorter ICU stays and lower mortality.[22] Pannach et al. showed a decreased need for all blood products in patients with GI bleeding who were taking NOACs as compared to those taking VKA while also showing a lower mortality among the NOAC patients.[23]

While our study did not show a difference in location of GI bleed between those taking NOACs and those taking VKAs, another study showed a larger percentage of lower GI bleeding in patients receiving NOAC in comparison to VKA.[23] Although proton pump inhibitors decreased the risk for GI bleeding by 50%, peptic disease was the etiology for bleeding in more than 60% of the patients in our study for both groups.[24]

Two patients treated with VKAs in our study were found to have intestinal wall hematomas. This was previously described in patients treated with VKAs. In our study there were no patients with NOAC treatment that had such hematomas.[25] While previous studies have shown a higher detection of malignancy among NOAC patients with GI bleeding, when compared to VKA, in our study the rate of polyps or neoplasms was not significantly different between the two groups (8% for NOAC vs.10% for VKA).[26]

In a sub-group analysis of our study, a Forest plot demonstrated a clear reduction in the risk of major/life-threatening GI bleeding in those treated with NOACs as compared to those treated with VKA for the sub-groups of age, gender, co-morbidities, and concomitant medication use. This is similar to data from a prior study, which showed an odds ratio for any severity of GI bleeding of 0.86 in NOAC patients as compared to those treated with VKAs (95% CI 1.00-0.73).[6]

The limitations of our study include the relatively lower number of patients treated with NOACs as this prevented adequate statistical comparison among patients receiving each individual NOAC. In addition, we did not search for Edoxaban use, as it is not widely used in Israel.

Our study did not evaluate the dose of each NOAC, the activity levels of NOACs, or the glomerular filtration rates of patients, which can influence NOAC clearance.[27]

Finally, reversal agents for NOACs have been developed in recent years, including Idarucizumab for Dabigatran reversal and other reversal agents such as Andexanet alfa and Aripazine.[10, 15] Our cohort of NOAC patients were not treated with reversal agents and only few of our patients were treated with prothrombin complex concentrates, corresponding to the current guidelines.[28]

In conclusion, data on the severity of GI bleeding among patients using different classes of anticoagulants may help to guide treatment decisions. While our study showed a lesser severity of GI bleeding among patients receiving NOAC therapy as compared to VKA, future prospective studies should compare these groups to determine what other patient characteristics may have an effect on GI bleeding, and determine if NOAC reversal agents can further decrease severity of GI bleeding.

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KEY SUMMARY

The established knowledge on this subject:

• Previous studies comparing the risk for gastrointestinal bleeding in patients receiving treatment with VKA in comparison to NOACs have shown conflicting results.

• Most of these studies relate only to the rate of GI bleeding events, with less information regarding the severity of bleeding, location of bleeding, and use of endoscopic management.

The significant new findings of this study

• Major bleeding events were seen significantly less in patients treated with NOACs in comparison to VKA.

• Packed red blood cell and fresh-frozen plasma transfusions were administered less in the NOAC patients as compared to the VKA patients. No statistically significant differences in length of hospitalization, re-bleeding, or mortality were seen between groups.

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