



Article

Characteristics, Location, and Clinical Outcomes of Gastrointestinal Bleeding in Patients Taking New Oral Anticoagulants Compared to Vitamin K Antagonists

A Reum Choe ¹, Chang Mo Moon ^{1,2,*}, Chung Hyun Tae ¹, Jaeyoung Chun ^{3,4}, Ki Bae Bang ⁵, Yoo Jin Lee ⁶, Hyun Seok Lee ⁷, Yunho Jung ⁸, Sung Chul Park ⁹ and Hoon Sup Koo ¹⁰

¹ Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul 07985, Korea; prems0121@naver.com (A.R.C.); jhtae@ewha.ac.kr (C.H.T.)

² Inflammation-Cancer Microenvironment Research Center, College of Medicine, Ewha Womans University, Seoul 07804, Korea

³ Department of Internal Medicine, Seoul National University College of Medicine, Liver Research Institute, Seoul 03080, Korea; J40479@gmail.com

⁴ Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul 06273, Korea

⁵ Department of Internal Medicine, Dankook University College of Medicine, Cheonan 31116, Korea; kibaebang@gmail.com

⁶ Department of Internal Medicine, Keimyung University School of Medicine, Daegu 42601, Korea; doctorlyj@dsmc.or.kr

⁷ Department of Internal Medicine, School of Medicine, Kyungpook National University, Kyungpook National University Hospital, Daegu 41404, Korea; lhsworld@nate.com

⁸ Department of Internal Medicine, Soonchunhyang University College of Medicine, Cheonan 31151, Korea; yoonho7575@naver.com

⁹ Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon 24289, Korea; schlp@hanmail.net

¹⁰ Department of Internal Medicine, Konyang University College of Medicine, Daejeon 35365, Korea; koo7574@naver.com

* Correspondence: mooncm27@ewha.ac.kr; Tel.: +82-2-2650-2945



Citation: Choe, A.R.; Moon, C.M.; Tae, C.H.; Chun, J.; Bang, K.B.; Lee, Y.J.; Lee, H.S.; Jung, Y.; Park, S.C.; Koo, H.S. Characteristics, Location, and Clinical Outcomes of Gastrointestinal Bleeding in Patients Taking New Oral Anticoagulants Compared to Vitamin K Antagonists. *J. Clin. Med.* **2021**, *10*, 2693. <https://doi.org/10.3390/jcm10122693>

Academic Editor: Mohammad H. Derakhshan

Received: 6 May 2021
Accepted: 10 June 2021
Published: 18 June 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract: New oral anticoagulants (NOACs) are commonly used in clinical practice as alternatives to vitamin K antagonists (VKA). However, the etiology, clinical course, and risk of gastrointestinal (GI) bleeding remain unclear. We aimed to evaluate the clinical characteristics and location of acute GI bleeding associated with NOACs and its severity and outcomes compared to VKA. This retrospective multicenter study included 381 subjects on anticoagulants who underwent appropriate diagnostic examination due to GI bleeding. Regarding the characteristics of acute GI bleeding, the proportion of vascular lesions was significantly lower in the NOACs group than that in the VKA group. Small bowel bleeding occurred less commonly in the NOACs group, but the difference did not reach statistical significance. Regarding severity and clinical outcomes, patients on NOACs received significantly smaller volumes of transfused blood products and had shorter ICU stays than those on VKA. Moreover, the need for surgery and the risk of rebleeding in the NOACs group were significantly lower than those in the VKA group. Patients on NOACs have better clinical outcomes in terms of severity of acute GI bleeding or rebleeding than patients on VKA. Patients on NOACs demonstrate different characteristics and location of acute GI bleeding than those on VKA.

Keywords: gastrointestinal bleeding; new oral anticoagulants; vitamin K antagonist; rebleeding

1. Introduction

Since the Food and Drug Administration (FDA) approved new oral anticoagulants (NOACs) in 2010 [1,2], direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (dabigatran) are now available in clinical practice [3,4]. The

2016 European Society of Cardiology guidelines recommended NOACs for patients with non-valvular atrial fibrillation (NVAF) to prevent stroke [5]. The 2016 American College of Chest Physician guideline and expert panel report also suggested a prescription in favor of NOACs to vitamin K antagonist (VKA) for the initial and long-term management of venous thromboembolism in patients without cancer [6].

The VKA inhibits vitamin K epoxide reductase, thereby attenuating the reduction of oxidized vitamin K in the liver. In contrast to VKA, the NOACs directly inhibit a single clotting enzyme; dabigatran inhibits thrombin, whereas rivaroxaban, apixaban, and edoxaban inhibit factor Xa [7,8]. The NOACs have major pharmacologic advantages over VKA, including fast onset/offset of action, few clinically relevant interactions with other drug and food, and predictable pharmacokinetics, simple administration by fixed doses without any monitoring [9–11].

Recently, several randomized clinical trials have shown that NOACs is preferred to VKA, due to its efficacy in preventing stroke and systemic embolisms in patients with NVAF [12–14]. NOACs have been reported to significantly decrease the prevalence of major bleeding, particularly the rates of intracranial hemorrhage and critical bleeding [4,15]. Moreover, several meta-analyses have shown that NOACs have a more favorable safety profile than VKA [16–19]. However, the risk of NOAC-associated bleeding, particularly gastrointestinal (GI) bleeding, is still a concern. The ROCKET AF trial [20], a comparative study of rivaroxaban and warfarin for the prevention of stroke and embolism, showed that patients treated with rivaroxaban had a significantly higher rate of GI bleeding than those treated with VKA. Contrarily, the XANTUS registry [21] investigated the stroke prevention effect of anticoagulants in patients with AF and showed that major GI bleeding occurred less frequently in the rivaroxaban group. To date, it remains unclear whether NOACs increases the risk of GI bleeding compared to warfarin. Moreover, few studies have reported the exact source and location of GI bleeding during NOACs treatment with comprehensive examination methods, including gastrointestinal endoscopy or abdominal pelvis computed tomography (CT).

Therefore, we aimed to assess the clinical and endoscopic features of acute GI bleeding in patients prescribed NOACs and evaluate the severity and clinical outcomes of these events compared to VKA.

2. Materials and Methods

2.1. Study Population

In this retrospective multicenter cohort study, we analyzed the clinical data of study subjects collected at eight tertiary medical institutions between January 2014 and October 2017 in the Republic of Korea. We included subjects who met the following three criteria: (1) patients who visited the hospital with symptoms of overt GI bleeding; (2) patients treated with anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban, and warfarin) for at least 3 months; (3) patients who underwent diagnostic esophagogastroduodenoscopy (EGD), colonoscopy, sigmoidoscopy, small bowel (SB) enteroscopy, or capsule endoscopy to identify the focus of GI bleeding, according to the diagnostic strategy of each hospital. Subjects were excluded in the following conditions: (1) those diagnosed with GI cancer before overt GI bleeding episode ($n = 95$); (2) GI ulcers within 6 months before starting anticoagulants ($n = 107$); (3) inflammatory bowel disease or intestinal Behçet's disease ($n = 9$); and (4) hematologic diseases with a bleeding tendency ($n = 23$). Finally, a total of 381 patients were included in this study (Figure 1). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee of all participating hospitals.

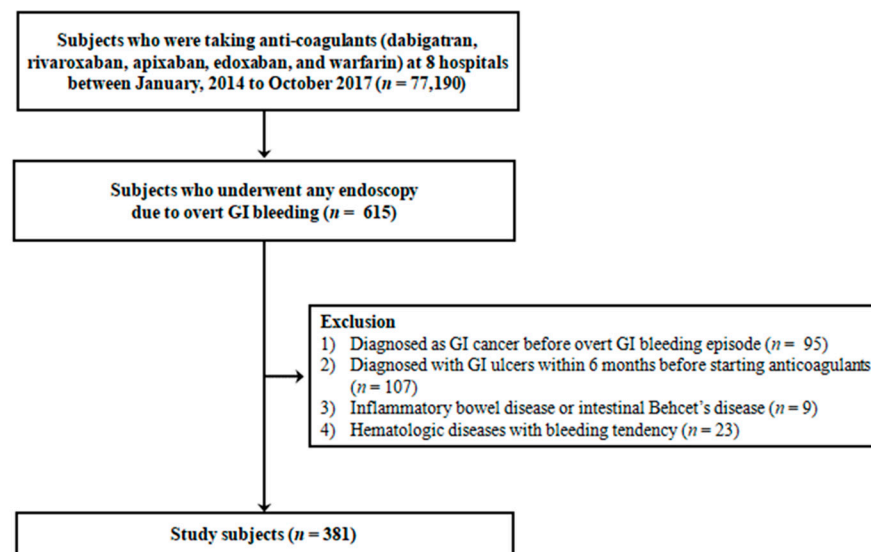


Figure 1. Flow diagram. A total of 615 patients who underwent any endoscopy due to overt GI bleeding were enrolled from eight large-volume university hospitals. Of these, 234 patients were excluded, and 381 patients were enrolled for analysis.

2.2. Data Collection and Definition of Variables

We collected the demographic, clinical, and laboratory data from the patients at the time of presentation. The baseline characteristics included the presence of major GI bleeding, history of prior GI bleeding, indication for anticoagulation, medical comorbidities, and any concomitant drugs associated with GI bleeding. The risk of major bleeding was calculated using the HAS-BLED (old age, drugs/alcohol intake, hypertension, abnormal liver/kidney function, stroke, bleeding predisposition or history, and labile international normalized ratio) scoring system including six comorbid conditions.

GI bleeding was identified from the medical records by the presence of hematemesis, melena, or hematochezia. Major bleeding was defined as fatal or symptomatic bleeding in a critical organ or bleeding that caused a decrease in hemoglobin level of 2 g/dL or more, leading to transfusion of 2 or more units of whole or red blood cells [22]. Location of GI bleeding was identified as upper GI, small bowel, lower GI, or indeterminate by reviewing endoscopic or radiologic records. The diagnostic modalities for identifying the causes of GI bleeding included EGD, colonoscopy/sigmoidoscopy, SB enteroscopy, capsule endoscopy, or abdominal pelvic computerized tomography (CT).

GI bleeding lesions were divided into four types according to the endoscopic characteristics: (1) vascular lesion (angiodyplasia, Dieulafoy's lesion, varices, gastric antral vascular ectasia, hemorrhoid, and ischemic colitis); (2) inflammatory lesion (esophagitis, gastritis, colitis, erosion, ulcer, and inflammatory bowel disease); (3) neoplastic lesion (polyp, tumor); (4) anatomic lesion and others (diverticulum, Mallory–Weiss syndrome, post-procedural bleeding after polypectomy, or endoscopic submucosal dissection).

Clinical outcomes were investigated by hemodynamic instability at the point of admission, need for angiographic or surgical intervention, in-hospital mortality, and rebleeding. Hemodynamic instability was defined as one or more out-of-range vital sign measurements, such as systolic blood pressure < 90 mmHg or heart rate > 100/min. Rebleeding was defined as endoscopic confirmation of newly developed GI bleeding or an explained drop in hemoglobin more than 2 g/dL after 7 days of initial endoscopic hemostasis treatment [23,24].

2.3. Statistical Analysis

Continuous variables were presented as mean \pm standard deviation, and categorical variables were presented as the number of subjects and percent. Group comparison was performed by using independent-samples t-tests or Mann–Whitney U-tests for continuous

variables and Pearson's chi-squared tests or Fisher's exact tests for categorical variables. The adjusted odds ratio for clinical outcomes was obtained by multivariable logistic-regression analysis adjusted for sex and HAS-BLED score. Any variable with a p -value < 0.2 in univariate analysis was accepted as a candidate for multivariate analysis along with variables with known clinical importance. Finally, statistical significance was considered as $p < 0.05$ with a two-tailed test. We used the analysis of covariance for the number of red blood cell transfusions, days in the hospital, and ICU days. The analyses were adjusted for sex and HAS-BLED score as continuous variables. All statistical analyses were performed using SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline Characteristics of Study Subjects

The baseline characteristics of the patients on NOACs or VKA who experienced acute GI bleeding are shown in Table 1. Among them, 144 patients were prescribed NOACs, and 237 patients used VKA (mean age; 77.9 ± 7.8 vs. 73.3 ± 11.9 years). Regarding indications for anticoagulation, NOACs were used for AF or atrial flutter in 108 cases (75.0%) and pulmonary embolism or deep vein thrombosis in 29 cases (20.1%). VKAs were used for AF or atrial flutter in 117 cases (49.4%) and prosthetic valves in 69 cases (29.1%). Twenty-five of 144 (17.3%) patients on NOACs concomitantly had antiplatelet agents (aspirin, clopidogrel), whereas 36 of 237 (15.2%) on VKA used antiplatelet agents. The concomitant use of proton pump inhibitor did not differ significantly between the two groups, while the use of H2 receptor antagonist showed more common in NOACs group. There was no difference in examination modalities between the two groups.

Table 1. Baseline characteristics of the patients prescribed with NOACs or VKA who experienced GI bleeding.

| | NOACs (<i>n</i> = 144) | VKA (<i>n</i> = 237) | <i>p</i> Value |
|--|----------------------------|--------------------------|----------------|
| Mean age, years (range) * | 77.9 ± 7.8 (54–95) | 73.3 ± 11.9 (29–95) | <0.001 |
| Male sex (%) | 63 (43.8%) | 122 (51.5%) | 0.071 |
| Mean body mass index * | 23.3 ± 3.8 | 22.1 ± 4.1 | 0.005 |
| History of smoking (%) | | | 0.187 |
| No | 124 (86.1%) | 186 (78.5%) | |
| Ex-smoker | 15 (10.4%) | 38 (16.0%) | |
| Current smoker | 5 (3.5%) | 13 (5.5%) | |
| History of alcohol intake (%) | | | 0.368 |
| No | 117 (81.3%) | 198 (83.5%) | |
| Social | 14 (9.7%) | 26 (11.0%) | |
| Heavy | 13 (9.0%) | 13 (5.5%) | |
| History of major bleeding † (%) | 17 (11.8%) | 26 (11.0%) | 0.903 |
| History of prior gastrointestinal bleeding (%) | 29 (20.1%) | 42 (17.7%) | 0.678 |
| Symptom (%) | | | 0.061 |
| Hematemesis | 25 (17.4%) | 43 (18.1%) | |
| Melena | 60 (41.7%) | 124 (52.3%) | |
| Hematochezia | 59 (41.0%) | 70 (29.5%) | |
| Indication for Anticoagulation (%) | | | |
| Atrial fibrillation/flutter | 108 (75.0%) | 117 (49.4%) | <0.001 |
| Pulmonary embolism/DVT | 29 (20.1%) | 40 (16.9%) | 0.329 |
| Prosthetic valve | 1 (0.7%) | 69 (29.1%) | <0.001 |
| Stroke prevention | 6 (4.2%) | 11 (4.6%) | 0.533 |
| Comorbidities (%) | | | |
| Congestive heart failure | 49 (34.0%) | 77 (32.5%) | 0.954 |
| Hypertension | 100 (69.4%) | 137 (57.8%) | 0.071 |
| Arrhythmia | 108 (75.0%) | 144 (60.8%) | 0.019 |

Table 1. Cont.

| | NOACs (n = 144) | VKA (n = 237) | p Value |
|---------------------------------------|--------------------|------------------|---------|
| Diabetes mellitus | 53 (36.8%) | 74 (31.2%) | 0.362 |
| Dyslipidemia | 31 (21.5%) | 42 (17.7%) | 0.460 |
| Coronary heart disease | 29 (20.1%) | 38 (16.0%) | 0.394 |
| Stroke | 52 (36.1%) | 58 (24.5%) | 0.028 |
| History of transient ischemic attack | 4 (2.8%) | 3 (1.3%) | 0.314 |
| Chronic kidney disease | 14 (9.7%) | 53 (22.4%) | 0.001 |
| Chronic obstructive pulmonary disease | 6 (4.2%) | 5 (2.1%) | 0.273 |
| Chronic hepatitis | 1 (0.7%) | 8 (3.4%) | 0.086 |
| Liver cirrhosis | 13 (9.0%) | 21 (8.9%) | 0.955 |
| Pulmonary embolism/DVT | 26 (18.1%) | 32 (13.5%) | 0.297 |
| Peripheral arterial occlusive disease | 3 (2.1%) | 13 (5.5%) | 0.094 |
| Prosthetic valve | 2 (1.4%) | 74 (31.2%) | <0.001 |
| Concomitant medications (%) | | | |
| Aspirin | 13 (9.0%) | 27 (11.4%) | 0.135 |
| Clopidogrel | 12 (8.3%) | 9 (3.8%) | 0.173 |
| NSAIDs | 5 (3.5%) | 18 (7.6%) | 0.080 |
| Steroid | 7 (4.9%) | 15 (6.3%) | 0.474 |
| Proton pump inhibitor | 29 (20.1%) | 35 (14.8%) | 0.233 |
| H2 receptor antagonist | 18 (12.5%) | 10 (4.2%) | 0.004 |
| Examination Modalities (%) | | | |
| Esophagogastroduodenoscopy | 43 (21.0%) | 52 (16.0%) | 0.116 |
| Colonoscopy/Sigmoidfibroscopy | 91 (44.4%) | 160 (49.2%) | 0.269 |
| SB enteroscopy | 0 (0.0%) | 3 (0.9%) | 0.294 |
| Capsule endoscopy | 12 (5.9%) | 24 (7.4%) | 0.591 |
| Abdomen pelvis CT | 59 (28.8%) | 86 (26.5%) | 0.440 |

NOACs, new oral anticoagulants; VKA, vitamin K antagonist; GI, gastrointestinal; DVT, deep vein thrombosis; NSAIDs, non-steroidal anti-inflammatory drugs; SB, small bowel; CT, computerized tomography; * Mean \pm standard deviation; † History of major bleeding defined by International Society on Thrombosis and Hemostasis as fatal bleeding or symptomatic bleeding in a critical organ, or bleeding causing a decrease in hemoglobin level of 2 g/dL or more, leading to transfusion of 2 or more units of whole blood or red blood cells.

3.2. Source, Lesion, and Location of Acute GI Bleeding in Patients on NOACs or VKA

The most common site of acute GI bleeding was the upper GI tract in the NOACs (51/144, 35.4%) and the VKA group (98/237, 41.4%). Small bowel bleeding was observed in 6/144 (4.2%) in the NOACs group and 16/237 (6.8%) in the VKA group. The prevalence of lower GI bleeding was 33/144 (22.9%) in the NOACs group and 43/237 (18.1%) in the VKA group.

Among the 90 patients on NOACs who experienced GI bleeding, the common causes of upper GI bleeding were benign gastric ulcer in 25 (27.8%) patients, duodenal ulcer in 5 (5.6%), gastric varix in 3 (3.3%), and Mallory–Weiss syndrome in 3 (3.3%) patients. The common causes of small bowel bleeding were vascular lesions in 4 (4.4%) and inflammatory lesions in 2 (2.2%) patients. The common causes of lower GI bleeding were rectal ulcer without exposed vessels in 8 (8.9%) patients, diverticuli without current bleeding in 7 (7.8%), and colon polyp bleeding in 5 (5.6%) patients. Among the 157 patients on VKA who experienced GI bleeding, the common causes of upper GI bleeding were benign gastric ulcer in 47 (29.9%) patients, duodenal ulcer in 14 (8.9%), and gastric angiodysplasia in 9 (5.7%) patients. The common causes of small bowel bleeding were inflammatory lesions in 9 (5.7%) and vascular lesions in 6 (3.8%) patients. The common causes of lower GI bleeding were hemorrhoid bleeding in 10 (6.4%) patients, colon polyp bleeding in 10 (6.4%), rectal ulcer without exposed vessels in 4 (2.5%), and diverticuli without current bleeding in 4 (2.5%) patients (Table 2).

Table 2. Sources of GI bleeding in patients with NOACs or VKA.

| | NOACs (n = 144) | VKA (n = 237) |
|--|-----------------|---------------|
| Upper GI findings (%) | 51 (35.4) | 98 (41.4) |
| Esophagus | 8 (5.6) | 13 (5.5) |
| Esophagitis | 2 (1.4) | 1 (0.4) |
| Esophageal ulcer | 1 (0.7) | 1 (0.4) |
| Mallory-Weiss syndrome | 3 (2.1) | 7 (3.0) |
| Esophageal angiodysplasia | 0 (0) | 1 (0.4) |
| Esophageal varix | 2 (1.4) | 3 (1.3) |
| Stomach | 38 (26.4) | 69 (29.1) |
| Gastric varix | 3 (2.1) | 1 (0.4) |
| Gastric antral vascular ectasia | 1 (0.7) | 2 (0.8) |
| Gastric erosion | 2 (1.4) | 3 (1.3) |
| Benign gastric ulcer | 25 (17.4) | 47 (19.8) |
| Gastric cancer | 2 (1.4) | 1 (0.4) |
| Gastric angiodysplasia | 2 (1.4) | 9 (3.8) |
| Gastric dieulafoy | 1 (0.7) | 6 (2.5) |
| Gastric polypectomy | 2 (1.4) | 0 (0) |
| Or endoscopic submucosal dissection bleeding | | |
| Duodenum | 5 (3.5) | 16 (6.8) |
| Duodenal ulcer | 5 (3.5) | 14 (5.9) |
| Duodenal angiodysplasia | 0 (0) | 1 (0.4) |
| Duodenal dieulafoy lesion | 0 (0) | 1 (0.4) |
| Duodenitis | 0 (0) | 0 (0) |
| Small bowel findings (%) | 6 (4.2) | 16 (6.8) |
| Inflammatory lesion | 2 (1.4) | 9 (3.8) |
| Neoplastic lesion | 0 (0) | 0 (0) |
| Vascular lesion | 4 (2.8) | 6 (2.5) |
| Others | 0 (0) | 1 (0.4) |
| Lower GI findings (%) | 33 (22.9) | 43 (18.1) |
| Vascular lesion | 5 (3.5) | 13 (5.5) |
| Hemorrhoid | 4 (2.8) | 10 (4.2) |
| Ischemic colitis | 1 (0.7) | 3 (1.3) |
| Anatomic lesion | 8 (5.6) | 7 (3.0) |
| Diverticuli without bleeding | 7 (4.9) | 4 (1.7) |
| Diverticuli with current bleeding | 1 (0.7) | 3 (1.3) |
| Inflammatory lesion | 14 (9.7) | 10 (4.2) |
| Rectal ulcer only | 8 (5.6) | 4 (1.7) |
| Rectal ulcer with exposed vessel | 1 (0.7) | 1 (0.4) |
| Colon ulcer | 3 (2.1) | 1 (0.4) |
| Infectious colitis | 1 (0.7) | 1 (0.4) |
| Pseudomembranous colitis | 1 (0.7) | 2 (0.8) |
| Inflammatory bowel disease | 0 (0) | 1 (0.4) |
| Neoplastic lesion | 6 (4.2) | 13 (5.5) |
| Colon polyp | 5 (3.5) | 10 (4.2) |
| Colon cancer | 1 (0.7) | 3 (1.3) |
| Unidentified lesion (%) | 54 (37.5) | 80 (33.8) |

GI, gastrointestinal; NOACs, new oral anticoagulants; VKA, vitamin K agonist.

Regarding the characteristics of GI bleeding in the two groups, the proportion of vascular lesions in the location of GI bleeding, bleeding in the small bowel occurred less commonly in patients on NOACs, but the difference could not reach statistical significance (6.7% vs. 10.2%, $p = 0.090$, $p = 0.038$). Regarding 0.090) (Table 3).

Table 3. Lesion characteristics and location of GI bleeding in patients with NOACs or VKA.

| | NOACs (N = 90) | VKA (N = 157) | p Value |
|-----------------------------------|----------------|---------------|---------|
| Lesion characteristics (%) | | | |
| Vascular lesion | 14 (15.6) | 40 (25.5) | 0.038 |
| Inflammatory lesion | 49 (54.4) | 81 (51.6) | 0.775 |
| Neoplastic lesion | 7 (7.8) | 14 (8.9) | 0.604 |
| Anatomic lesion & Others * | 20 (22.2) | 22 (14.0) | 0.638 |
| Location (%) | | | |
| Esophagus | 8 (8.9) | 13 (8.3) | 0.912 |
| Stomach | 38 (42.2) | 69 (43.9) | 0.334 |
| Duodenum | 5 (5.6) | 16 (10.2) | 0.284 |
| Small bowel | 6 (6.7) | 16 (10.2) | 0.090 |
| Colon | 33 (36.7) | 43 (27.4) | 0.460 |

NOACs, new oral anticoagulants; VKA, vitamin K agonist. * Others category was included diverticular bleeding, Mallory-Weiss syndrome, post polypectomy bleeding, and post endoscopic submucosal dissection bleeding.

3.3. Comparison of Clinical Outcomes in Patients on NOACs vs. VKA

Regarding clinical outcomes, patients treated with NOACs received significantly smaller volumes of blood transfusions with packed red blood cells than those taking VKA (2.1 ± 0.3 vs. 3.1 ± 0.2 , $p = 0.009$). Patient treated with NOACs stayed in ICU significantly shorter than those taking VKA (0.5 ± 0.2 vs. 1.0 ± 0.2 , $p = 0.049$). However, there was no significant difference in the stay of hospital between patients treated NOACs and VKA (9.0 ± 1.2 vs. 10.4 ± 0.9 , $p = 0.344$) (Figure 2).

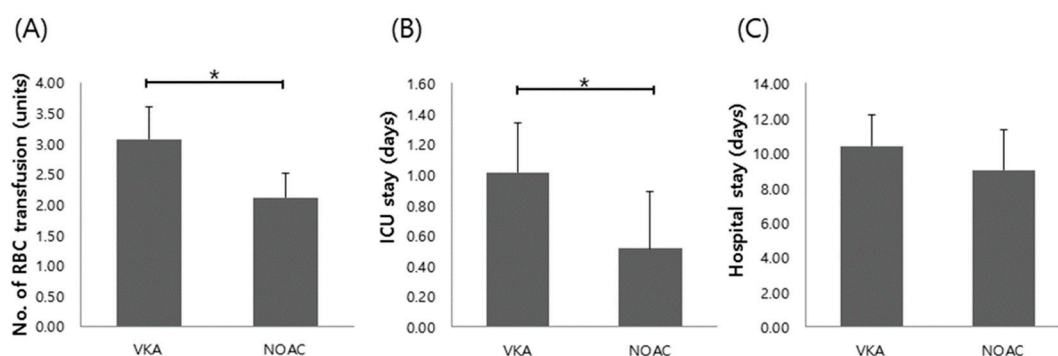


Figure 2. Clinical outcomes related to the severity of GI bleeding in patients on NOACs vs. VKA (A) number of red blood cell transfusion, (B) duration of ICU stay, (C) duration of hospital stay in patients treated with VKA and NOACs. * $p < 0.05$. VKA, vitamin K antagonist; NOAC, new oral anticoagulants; RBC, red blood cell; ICU, intensive care unit.

In multivariate analysis adjusted for sex and HAS-BLED scores, rebleeding was less common in patients on NOACs than in those on VKA (adjusted OR 0.42, 95% CI 0.22–0.79, $p = 0.007$). Regarding the need for surgery, a very low number of patients required a surgical intervention in both group (1 case in NOAC group and 4 cases in VKA group). There was no significant difference in hemodynamic instability at admission, the need for angiography, and mortality during hospitalization between the two groups (Table 4).

Table 4. Comparison of clinical outcomes in the patients with NOACs vs. VKA.

| Clinical Outcomes | NOACs (%) (n = 59) | VKA (%) (n = 123) | Multivariate Logistic Regression Analysis * | |
|--------------------------------------|-----------------------|----------------------|---|---------|
| | | | Adjusted OR (95% CI) | p Value |
| Hemodynamic instability at admission | 26 (17.7%) | 50 (21.6%) | 0.81 (0.47–1.37) | 0.167 |
| Rebleeding | 15 (10.6%) | 46 (20.9%) | 0.42 (0.22–0.79) | 0.007 |
| Need for angiography | 11 (8.1%) | 12 (5.6%) | 1.47 (0.62–3.45) | 0.112 |
| Mortality during Hospital day | 6 (4.1%) | 11 (4.7%) | 0.84 (0.30–2.35) | 0.729 |
| Need for surgery † | 1 (0.7%) | 4 (1.7%) | 0.82 (0.69–0.98) | 0.045 |

NOACs, new oral anticoagulants; VKA, vitamin K agonist; OR, odds ratio; CI, confidence interval; * These odds ratios and 95% CIs were adjusted for sex, HAS-BLED score; † The type of surgery in patient with NOACs was distal gastrectomy. The patients with VKA underwent distal gastrectomy (2 cases), small bowel segmental resection (1 case), and right hemicolectomy (1 case).

We analyzed the clinical outcomes in the patients associated with different NOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban. Consequently, unfavorable clinical outcomes such as hemodynamic instability at admission, need for angiography or surgery, mortality during hospital days, and rebleeding were the most frequent in those with rivaroxaban compared with other NOACs (Table 5).

Table 5. The clinical outcomes in the patients associated with different NOACs.

| Outcomes | NOACs | Dabigatran (n = 32, 22.2%) | Rivaroxaban (n = 72, 50.0%) | Apixaban (n = 28, 19.5%) | Edoxaban (n = 12, 8.3%) |
|--------------------------------------|-------|-------------------------------|--------------------------------|-----------------------------|----------------------------|
| Hemodynamic instability at admission | | 5 (19.3%) | 13 (50.0%) | 7 (26.9%) | 1 (3.8%) |
| Need for angiography | | 3 (27.3%) | 7 (63.7%) | 1 (9.0%) | 0 (0.0%) |
| Need for surgery | | 0 (0.0%) | 1 (100.0%) | 0 (0.0%) | 0 (0.0%) |
| Mortality during Hospital day | | 1 (16.7%) | 4 (66.6%) | 1 (16.7%) | 0 (0.0%) |
| Rebleeding | | 2 (13.3%) | 9 (60.0%) | 4 (26.7%) | 0 (0.0%) |

NOACs, new oral anticoagulants.

4. Discussion

In the present study, patients treated with NOACs who experienced acute GI bleeding had different characteristics and clinical outcomes than those treated with VKA. The proportion of vascular lesions and small bowel bleeding was lower in the NOACs group than that in the VKA group. The clinical outcomes in terms of severity and rebleeding are better in the NOACs group than in the VKA group.

Patients on NOACs who experienced GI bleeding had fewer unfavorable outcomes such as critical bleeding events requiring blood transfusion or rebleeding than those on VKA. Our results suggest that acute GI bleeding associated with NOACs may be less severe than that associated with VKA, which may be explained by the short half-life of NOACs (NOACs around 8–14 h, VKA 36–42 h) [1,25]. Therefore, the cessation of NOACs leads to a return of the coagulant function and recovery in a short period [26]. If GI bleeding is recognized, discontinuation of NOACs can quickly attenuate their anticoagulation effect. Moreover, this difference in the results achieved with NOACs and VKA was due to the potentially dangerous overdosing of VKA, which frequently occurs in clinical settings [27–29]. VKA have a large number of food or drug interactions, which complicate its anticoagulation effect [30]. Especially, acute illness such as infection and organ failure can prolong the international normalized ratios (INRs) in patients on VKA [31]. The intrinsic difficulty in maintaining therapeutic levels in those treated with VKA results in supra-therapeutic INRs and a risk of severe bleeding [32]. Therefore, the difference in severity and outcomes of acute GI bleeding between NOACs and VKA may be explained by their pharmacological properties.

In this study, regarding the location of GI bleeding, bleeding in the small bowel occurred less common in patients on NOACs, but the difference could not reach statistical

significance. Generally, bleeding in the small bowel remains relatively rare, accounting for 5–10% of all patients with GI bleeding [33]. Bleeding originated from the small bowel in 6 (6.7%) patients on NOACs and 16 (10.2%) patients on VKA in our study. Likewise, Diamantopoulou, et al. presented that the site of bleeding was located in the small bowel in 2/43 of NOAC patients and 6/68 of warfarin group [34]. Another cohort study also reported that GI bleeding associated with the use of dabigatran was more common from a source distal to the ligament of Treitz [35]. The pathophysiological explanation may relate to a low bioavailability of dabigatran [36]. Despite the similar mode of action, bioavailability differs according to the NOACs (dabigatran, 3–7%; apixaban, 50–60%; edoxaban, 62%; rivaroxaban 66–100%). The incidence of small bowel bleeding varies depending on the type or dosage of NOACs. This difference in results may be influenced by the type or dosage of NOACs and the characteristics of the study subjects. Therefore, further large-scale prospective studies are warranted to evaluate small bowel bleeding between these four NOACs.

In our cohort, vascular lesions were less common in patients on NOACs than in those on VKA. Pathophysiologically, NOACs is a non-absorbed, active anticoagulant within the GI tract lumen and promotes GI bleeding from vulnerable mucosal erosions [37]. Considering this characteristic, the use of NOACs may have no significant effect on intact mucosal lesions such as hemorrhoids, but can trigger bleeding in vulnerable mucosal lesions such as erosions or ulcers. These results may help to predict and prevent acute GI bleeding and evaluate the patients' existing GI conditions before prescribing anticoagulants. In a recent network meta-analysis, apixaban had the highest probability to be the safest option with regard to the risk of GI bleeding, followed by edoxaban, warfarin, dabigatran, and rivaroxaban [38].

Our study has limitations. First, this study was conducted in an observational and retrospective manner, which may limit the generalization of its results and cause potential bias. It is impossible to completely control confounding factors such as comorbidities and medications that can affect acute GI bleeding. However, we tried to reduce this effect by adjusting for sex and HAS-BLED scores as confounding variables in our multivariate analysis. Second, diagnostic tests for GI bleeding such as EGD, colonoscopy, sigmoidoscopy, capsule endoscopy, SB enteroscopy, and abdomen pelvis CT were not equally performed in all patients. Also, some diagnostic modalities were not conducted in some subjects. However, as the eight institutions participating in this study were tertiary referral hospitals, the diagnostic strategy for acute overt GI bleeding was relatively similar. Third, due to the retrospective study design, there was a limitation in analyzing the acute changes just before GI bleeding, which could affect events.

Despite these limitations, our study had the following advantages. It showed the source of acute GI bleeding in NOACs, examined by endoscopic and imaging modalities. Moreover, we compared the clinical severity and outcomes of acute GI bleeding between NOACs and VKA by analyzing a relatively large amount of patient data.

5. Conclusions

Acute GI bleeding in patients on NOACs showed favorable clinical outcomes, such as the need for transfusion or surgery and rebleeding than in patients on VKA. Further, the characteristics and location of acute GI bleeding lesions differed between the NOACs and VKA group. Our results may help to determine the diagnostic and therapeutic approaches when physicians encounter acute GI bleeding events in patients on anticoagulants.

Author Contributions: Conceptualization, C.M.M. and A.R.C.; Funding acquisition, C.M.M.; Investigation, A.R.C., C.H.T., J.C., Y.J. and H.S.K.; Methodology, C.M.M.; Project administration, A.R.C. and C.M.M.; Resources, Y.J.L. and H.S.L.; Software, C.H.T., J.C., K.B.B., Y.J.L., H.S.L., S.C.P. and H.S.K.; Supervision, C.M.M.; Visualization, Y.J. and S.C.P.; Writing—original draft, A.R.C.; Writing—review & editing, C.M.M., C.H.T., J.C. and K.B.B. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (2020R1A2C1010786 and 2020R1A5A2019210; Chang Mo Moon).

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Ewha Womans University Mokdong Hospital (EUMC 2017-11-026 and 2017-12-07), Seoul National University Hospital (H-2012-171-1185 and 2021-01-07), Dankook University Hospital (DKUH 2018-07-002 and 2018-07-19), Keimyung University Dongsan Medical Center (DSMC 2020-12-066 and 2020-12-28), Kyungpook National University Chilgok Hospital (KNUCH 2018-08-013 and 2018-08-10), Soonchunhyang University Hospital (SCHCA 2018-03-004 and 2018-03-28), Kangwon National University Hospital (KNUH 2018-08-009-001 and 2018-10-29), and Konyang University Hospital (KYUH 2018-07-019 and 2018-07-25).

Informed Consent Statement: Patient consent was waived due to the study's retrospective nature.

Data Availability Statement: The datasets generated and/or analyzed during the current study are not publicly available due to our IRB policy.

Acknowledgments: I would like to express my special thanks to Jung Min Moon and Hosim Soh at the Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea, for their assistance and effort.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

- Mekaj, Y.H.; Mekaj, A.Y.; Duci, S.B.; Miftari, E.I. New oral anticoagulants: Their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther. Clin. Risk. Manag.* **2015**, *11*, 967–977. [[CrossRef](#)]
- Greevy, T.; Kumar, K.K.; Jayaprakash, K. A review on novel oral anticoagulants. *Hygeia J. D Med.* **2015**, *7*, 51–56.
- Kuznetsov, S.; Barcelona, R.; Josephson, R.A.; Mohan, S.K.M. The Role of Nonvitamin K Antagonist Oral Anticoagulants (NOACs) in Stroke Prevention in Patients with Atrial Fibrillation. *Curr. Neurol. Neurosci. Rep.* **2016**, *16*. [[CrossRef](#)]
- Yao, X.; Abraham, N.S.; Sangaralingham, L.R.; Belloio, M.F.; McBane, R.; Shah, N.D.; Noseworthy, P.A. Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. *J. Am. Heart Assoc.* **2016**, *5*. [[CrossRef](#)] [[PubMed](#)]
- Kirchhof, P.; Benussi, S.; Kotecha, D.; Ahlsson, A.; Atar, D.; Casadei, B.; Castella, M.; Diener, H.C.; Heidbuchel, H.; Hendriks, J.; et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur. Heart J.* **2016**, *37*, 2893–2962. [[CrossRef](#)]
- Kearon, C.; Akl, E.A.; Ornelas, J.; Blaivas, A.; Jimenez, D.; Bounameaux, H.; Huisman, M.; King, C.S.; Morris, T.A.; Sood, N.; et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* **2016**, *149*, 315–352. [[CrossRef](#)] [[PubMed](#)]
- Ingrasciotta, Y.; Crisafulli, S.; Pizzimenti, V.; Marcianò, I.; Mancuso, A.; Andò, G.; Corrao, S.; Capranzano, P.; Trifirò, G. Pharmacokinetics of new oral anticoagulants: Implications for use in routine care. *Expert Opin. Drug Metab. Toxicol.* **2018**, *14*, 1057–1069. [[CrossRef](#)] [[PubMed](#)]
- Yeh, C.H.; Hogg, K.; Weitz, J.I. Overview of the new oral anticoagulants: Opportunities and challenges. *Arterioscler. Thromb. Vasc. Biol.* **2015**, *35*, 1056–1065. [[CrossRef](#)]
- Ciurus, T.; Sobczak, S.; Cichocka-Radwan, A. New oral anticoagulants—A practical guide. *Kardiochir. Torakochirurgia Pol.* **2015**, *12*, 111–118.
- Helms, T.M.; Silber, S.; Schäfer, A.; Masuhr, F.; Palm, F.; Darius, H.; Schrör, K.; Bänsch, D.; Bramlage, P.; Hankowitz, J.; et al. Consensus statement: Management of oral anticoagulation for stroke prevention in patients with nonvalvular atrial fibrillation. *Herzschrittmacherther Elektrophysiol.* **2016**, *27*, 295–306. [[CrossRef](#)]
- Senoo, K.; Lip, G. Comparative Efficacy and Safety of the Non-Vitamin K Antagonist Oral Anticoagulants for Patients with Nonvalvular Atrial Fibrillation. *Semin. Thromb. Hemost.* **2015**, *41*, 146–153. [[CrossRef](#)]
- Connolly, S.J.; Ezekowitz, M.D.; Yusuf, S.; Eikelboom, J.; Oldgren, J.; Parekh, A.; Pogue, J.; Reilly, P.A.; Themeles, E.; Varrone, J.; et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *N. Engl. J. Med.* **2009**, *361*, 1139–1151. [[CrossRef](#)]
- Granger, C.B.; Alexander, J.H.; McMurray, J.J.; Lopes, R.D.; Hylek, E.M.; Hanna, M.; Al-Khalidi, H.R.; Ansell, J.; Atar, D.; Avezum, A.; et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N. Engl. J. Med.* **2011**, *365*, 981–992. [[CrossRef](#)]
- Koretsune, Y.; Yamashita, T.; Yang, Y.; Chen, S.A.; Chung, N.; Giugliano, R.P. Edoxaban versus warfarin in east-asian (including Japanese) patients with atrial fibrillation—An engage AF-TIMI 48 sub-analysis. *Circ. J.* **2016**, *80*, 860–869.

15. Caldeira, D.; Barra, M.; Pinto, F.J.; Ferreira, J.J.; Costa, J. Intracranial hemorrhage risk with the new oral anticoagulants: A systematic review and meta-analysis. *J. Neurol.* **2015**, *262*, 516–522. [[CrossRef](#)]
16. Skaistis, J.; Tagami, T. Risk of Fatal Bleeding in Episodes of Major Bleeding with New Oral Anticoagulants and Vitamin K Antagonists: A Systematic Review and Meta-Analysis. *PLoS ONE* **2015**, *10*, e0137444. [[CrossRef](#)]
17. Katsanos, A.H.; Schellinger, P.D.; Köhrmann, M.; Filippatou, A.; Gurol, M.E.; Caso, V.; Paciaroni, M.; Perren, F.; Alexandrov, A.V.; Tsvigoulis, G. Fatal oral anticoagulant-related intracranial hemorrhage: A systematic review and meta-analysis. *Eur. J. Neurol.* **2018**, *25*, 1299–1302. [[CrossRef](#)]
18. Almutairi, A.R.; Zhou, L.; Gellad, W.F.; Lee, J.K.; Slack, M.K.; Martin, J.R.; Lo-Ciganic, W.H. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants for atrial fibrillation and venous thromboembolism: A systematic review and meta-analyses. *Clin. Ther.* **2017**, *39*, 1456–1478. [[CrossRef](#)]
19. Caldeira, D.; Rodrigues, F.B.; Barra, M.; Santos, A.T.; de Abreu, D.; Gonçalves, N.; Pinto, F.J.; Ferreira, J.J.; Costa, J. Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: A systematic review and meta-analysis. *Heart* **2015**, *101*, 1204–1211. [[CrossRef](#)]
20. Patel, M.R.; Mahaffey, K.W.; Garg, J.; Pan, G.; Singer, D.E.; Hacke, W.; Breithardt, G.; Halperin, J.L.; Hankey, G.; Piccini, J.P.; et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N. Engl. J. Med.* **2011**, *365*, 883–891. [[CrossRef](#)]
21. Camm, A.J.; Amarenco, P.; Haas, S.; Hess, S.; Kirchhof, P.; Kuhls, S.; Van Eickels, M.; Turpie, A.G. XANTUS: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur. Hearth J.* **2016**, *37*, 1145–1153. [[CrossRef](#)]
22. Schulman, S.; Kearon, C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J. Thromb. Haemost* **2005**, *3*, 692–694.
23. Chahal, D.; Lee, J.G.; Ali-Mohamad, N.; Donnellan, F. High rate of re-bleeding after application of Hemospray for upper and lower gastrointestinal bleeds. *Dig. Liver Dis.* **2020**, *52*, 768–772. [[CrossRef](#)]
24. Wetwittayakhleng, P.; Wonglhow, J.; Netinatsunton, N.; Chamroonkul, N.; Piratvisuth, T. Re-bleeding and its predictors after capsule en-doscopy in patients with obscure gastrointestinal bleeding in long-term follow-up. *BMC Gastroenterol.* **2019**, *19*, 216. [[CrossRef](#)] [[PubMed](#)]
25. Beyer-Westendorf, J.; Förster, K.; Pannach, S.; Ebertz, F.; Gelbricht, V.; Thieme, C.; Michalski, F.; Köhler, C.; Werth, S.; Sahin, K.; et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: Results from the Dresden NOAC registry. *Blood* **2014**, *124*, 955–962. [[CrossRef](#)] [[PubMed](#)]
26. Lee, J.H.; Lim, H.E.; Lim, W.-H.; Ahn, J.; Cha, M.-J.; Park, J.; Lee, K.H.; Park, H.-C.; Choi, E.-K.; Joung, B. The 2018 Korean Heart Rhythm Society Practical Guidelines on the use of Non-Vitamin K-Antagonist Oral Anticoagulants: Bleeding Control and Perioperative Management. *Korean J. Med.* **2019**, *94*, 40–56. [[CrossRef](#)]
27. Suh, D.-C.; Nelson, W.W.; Choi, J.C.; Choi, I. Risk of Hemorrhage and Treatment Costs Associated with Warfarin Drug Interactions in Patients with Atrial Fibrillation. *Clin. Ther.* **2012**, *34*, 1569–1582. [[CrossRef](#)] [[PubMed](#)]
28. Snipelisky, D.; Kusumoto, F. Current strategies to minimize the bleeding risk of warfarin. *J. Blood Med.* **2013**, *4*, 89–99. [[CrossRef](#)]
29. Pannach, S.; Goetze, J.; Marten, S.; Schreier, T.; Tittl, L.; Beyer-Westendorf, J. Management and outcome of gastrointestinal bleeding in patients taking oral anticoagulants or antiplatelet drugs. *J. Gastroenterol.* **2017**, *52*, 1211–1220. [[CrossRef](#)]
30. Vranckx, P.; Valgimigli, M.; Heidbuchel, H. The Significance of Drug–Drug and Drug–Food Interactions of Oral Anticoagulation. *Arrhythmia Electrophysiol. Rev.* **2018**, *7*, 55–61. [[CrossRef](#)]
31. Walborn, A.; Williams, M.; Fareed, J.; Hoppensteadt, D. International Normalized Ratio Relevance to the Observed Coagulation Abnormalities in Warfarin Treatment and Disseminated Intravascular Coagulation. *Clin. Appl. Thromb.* **2018**, *24*, 1033–1041. [[CrossRef](#)]
32. Brodie, M.M.; Newman, J.C.; Smith, T.; Rockey, D.C. Severity of Gastrointestinal Bleeding in Patients Treated with Direct-Acting Oral Anticoagulants. *Am. J. Med.* **2018**, *131*, 573. [[CrossRef](#)]
33. Gerson, L.B.; Fidler, J.L.; Cave, D.R.; Leighton, J.A. ACG Clinical Guideline: Diagnosis and Management of Small Bowel Bleeding. *Am. J. Gastroenterol.* **2015**, *110*, 1265–1287. [[CrossRef](#)]
34. Diamantopoulou, G.; Konstantakis, C.; Skroubis, G.; Theocharis, G.; Theopistos, V.; Triantos, C.; Thomopoulou, K. Acute Lower Gastrointestinal Bleeding in Patients Treated with Non-Vitamin K Antagonist Oral Anticoagulants Compared With Warfarin in Clinical Practice: Characteristics and Clinical Outcome. *Gastroenterol. Res.* **2019**, *12*, 21–26. [[CrossRef](#)]
35. Desai, J.; Kolb, J.M.; Weitz, J.I.; Aisenberg, J. Gastrointestinal bleeding with the new oral anticoagulants—defining the issues and the management strategies. *Thromb. Haemost.* **2013**, *110*, 205–212. [[CrossRef](#)]
36. Black, S.A.; Cohen, A.T. Anticoagulation strategies for venous thromboembolism: Moving towards a personalised approach. *Thromb. Haemost.* **2015**, *114*, 660–669.
37. Hakeam, H.A.; Al-Sanea, N. Effect of major gastrointestinal tract surgery on the absorption and efficacy of direct acting oral anticoagulants (DOACs). *J. Thromb. Thrombolysis* **2017**, *43*, 343–351. [[CrossRef](#)]
38. Guo, W.Q.; Chen, X.H.; Tian, X.Y.; Li, L. Differences in Gastrointestinal Safety Profiles Among Novel Oral Anticoagulants: Evidence from a Network Meta-Analysis. *Clin. Epidemiol.* **2019**, *11*, 911–921. [[CrossRef](#)]