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Severity of gastrointestinal bleeding is similar between patients receiving direct oral anticoagulants or vitamin K antagonists

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Keywords: Gastrointestinal bleeding. Direct oral anticoagulants. Vitamin K antagonists. Rivaroxaban. Dabigatran. Apixaban. Edoxaban.

Abbreviations used in this paper: CKD, chronic kidney disease, DOAC, direct oral anticoagulants; ED, Emergency Department; CT computed tomography; GIB, gastrointestinal bleeding; GFR: glomerular filtration rate; Hb, haemoglobin; NVAF, non-valvular atrial fibrillation; PRBC, packed red blood cells; VKA, vitamin K antagonists.

Conflict of interest: Luis Alcalá, César Jiménez, María Cerdá, Erik Johansson, Alba Jiménez, Amparo Santamaría, Carmen Alonso-Cotoner declare no conflicts of interest. Vicente Cortina has received consultancy/speaker fees from Werfen, and Diagnostic Grifols; Pavel Olivera serves as a consultant or advisory board Bayer, Pfizer, Boehringer Ingelheim, Amgen, Daiichi Sankyo and Techdow, and has received consultancy/speaker fees from Boehringer Ingelheim, Bayer, Daiichi Sankyo, Amgen; Amparo Santamaria Ortiz has received advisory fees for conferences from Daiichi Sankyo, Inc.; Bayer; Boehringer Ingelheim; Bristol Myers Squibb; and Pfizer.

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ABSTRACT

Background: Gastrointestinal bleeding (GIB) is a common adverse event related to anticoagulation therapy. However, evidence comparing the severity, aetiology, and outcomes of GIB in patients taking direct oral anticoagulants (DOAC) *vs*. vitamin K antagonists (VKA) is scarce.

AIMS: To evaluate the severity, aetiology and outcomes of GIB in patients under DOACs compared to VKA.

Methods: Patients under oral anticoagulant therapy admitted to the emergency department with acute GIB were prospectively recruited from July 2016 to January 2018 at a tertiary referral hospital. Demographic and clinical outcomes were obtained from medical records. Severity of the GIB event was classified as mild, major or severe according to clinical presentation and type of support needed. Aetiology and location of bleeding, number of packed red blood cells transfused (PRBC) and length of hospital stay were recorded until discharge or in-hospital death.

Results: A total of 208 patients with acute GIB under oral anticoagulant treatment were recruited: 119 patients on VKA, and 89 patients on DOAC with similar characteristics. Thirty-one patients had severe GIB; 134 major and 43 mild, with no differences in severity, number of PRBC and length of hospital stay between groups. Peptic disease was the most frequent aetiology of GIB in patients on VKA (20.2 % *vs.* 13.6%, p=0.20). Diverticular bleeding was the most frequent in patients on DOAC (14.3% *vs.* 24.8%, p= 0.056).

Conclusions: Severity and clinical outcomes of GIB are similar between patients on DOAC and patients on VKA, regardless of aetiology of GIB.

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INTRODUCTION

Gastrointestinal bleeding (GIB) is one of the most common medical emergencies, and a common adverse event related to anticoagulation therapy (1).

Direct oral anticoagulants (DOAC) have emerged as an alternative to the use of vitamin K antagonists (VKA), and seem to have a similar efficacy in the prevention of thromboembolic complications, a better profile in reducing the risk of intracranial haemorrhage and likely all-cause mortality, but higher rates of GIB (2,3,4). GIB is in fact one of the most common serious complications related to DOAC use, and the estimated risk of GIB in patients treated with anticoagulants is around 5% per year (4). In addition, meta-analyses of pivotal randomized control studies on patients with nonvalvular atrial fibrillation (NVAF) suggest that DOAC could be associated with higher risk of GIB, when compared to VKA (5). However, there is little evidence regarding the severity of GIB episodes and outcomes in patients receiving DOAC compared to VKA in a real-life setting. Hence, we aimed to evaluate the severity, aetiology and clinical outcomes of GIB in patients admitted to the emergency department (ED) under anticoagulant therapy with DOAC, compared to VKA.

METHODS

Participants

We prospectively recruited consecutive adult patients under oral anticoagulants presenting with acute GIB to the ED at a tertiary referral hospital from July 2016 to January 2018. Inclusion criteria were: overt acute GIB presenting as melena, haematochezia or hematemesis, age older than 18 years, and active treatment with DOAC or VKA. Exclusion criteria were patients on subcutaneous anticoagulants, and GIB due to acute ischemia or inflammatory bowel disease.

The study protocol (ASO-DAB-2014-01) was approved by the Ethics Committee at Hospital Universitari Vall d'Hebron. Written informed consent was obtained from each participant.

Clinical characterization

A complete medical history and physical examination were performed by the ED physicians. The presence of chronic kidney disease (CKD) was defined according to glomerular filtration rate (GFR) as moderate CKD if GFR 30-59 mL/min, and as severe CKD if GFR <30 mL/min. Patient management was provided by a multidisciplinary team including ED, haematologists and gastroenterologists. Data on comorbidities and current medication were collected from the patient's medical records.

Laboratory values were obtained from the first set of blood tests drawn upon presentation. The haemoglobin (Hb) drop was calculated after subtracting Hb on admission from the last known Hb value from patient's medical records.

Severity of GIB was defined as follows: 1) Severe GIB: patients hemodynamically unstable upon presentation; 2) Major GIB: decrease in the Hb level of at least 2 g/dl or transfusion of at least two packed red blood cells (PRBC) and 3) Mild GIB: All non-severe nor major bleeds.

Outcomes evaluated during hospitalization were the number of PRBC transfused, the length of hospital stay, and in-hospital mortality. Patients were followed-up until discharge or in-hospital death.

The origin of GIB was classified after endoscopic and radiologic studies, in upper GIB, lower GIB or obscure GIB if no bleeding location could be found.

Statistical analysis

Data are expressed as mean ± standard deviation or percentage (%), unless otherwise stated. For categorical variables, between-group differences were calculated by Chi-square test or Fisher's exact test. For quantitative variables, between-group differences were analysed using Student's *t* test. Non-parametric tests (Mann-Whitney U test, Wilcoxon Signed Ranks test) were used when needed. All data were analysed using commercial software SPSS 20.0, IBM Corp., Armonk, NY, USA.

RESULTS

Participants

During the study period, 230 patients presenting with GIB under anticoagulation therapy were admitted to our ED from which 22 were excluded **(Figure 1)**. A total of 208 patients were finally included: 119 patients on VKA, and 89 patients on DOAC. The DOAC group included 36 (40.4%) patients on apixaban, 29 (32.5%) on rivaroxaban, 19 (21.3%) on dabigatran, and 5 (5.8%) on edoxaban. The VKA group included 112 (94.1%) patients on acenocumarol, and seven (3.4%) on warfarin. Demographic and clinical characteristics of included patients are shown in **table 1**. Severe CKD (GFR<30 mL/min) was more prevalent in VKA (17% *vs*. 6.5% p=0.023), while history of previous cerebrovascular events was more prevalent in patients on DOAC (VKA 10% *vs.* DOAC 32% p= 0.024). When evaluating concomitant medication, amiodarone use was more common in patients on DOAC (VKA 4.2% *vs.* DOAC 12.5% p= 0.020).

Location and aetiology of bleeding

Location of GIB was identified in 184 (88.5%), being lower GIB the most common location in both groups. However, in terms of aetiology, a trend was observed when analysing diverticular bleeding, being more frequent in patients on DOAC (VKA 14.3% *vs.* DOAC 24.8% p=0.056). Bleeding location remained unknown in 24 (11.5%) patients, and catalogued as obscure GIB in 14 (11.8%) patients on VKA, and 10 (11.2%) on DOAC. The most common aetiology of GIB was peptic ulcer disease (20.2%) in patients on VKA, and diverticular bleeding (24.7%) in patients on DOAC (**Table 2).**

Clinical Outcomes

There were no differences on the Hb level on admission (VKA 9.5±2.7 g/dL *vs.* DOAC 9.1±2.5 g/dL; p =0.33), the drop of Hb (VKA 2.7±2.2 g/dL *vs*. DOAC 3.0±2.0 g/dL p = 0.25), the number of PRBC units transfused (VKA 2.2 ± 2.6 *vs.* DOAC 2.3 ± 2.6 p= 0.74) and the number of days in hospital (VKA 9.6 ± 8.2 *vs*. DOAC 9.5 ± 7.5 days, p= 0.41).

Seven (3.4%) patients died during hospitalization: four (3.4%) patients on VKA and three (3.4%) on DOAC. All died of acute respiratory failure: three due to nosocomial pneumonia, and four due to acute pulmonary oedema. Three thromboembolic events occurred during hospitalization: two (2.2%) on the DOAC group (one pulmonary thromboembolism and one embolic stroke), and one (0.8%) on the VKA group (non-lethal embolic stroke). Oral anticoagulants had been stopped, and all three patients were receiving treatment with low molecular weight heparin (prophylactic doses).

Severity of gastrointestinal bleeding

On admission, 31 (14.9%) patients presented as severe GIB: 19 (9.1 %) on VKA, and 12 (5.7 %) on DOAC; 134 as major GIB (64.3%): 71 (34.1%) on VKA, and 63 (30.2%) on DOAC and 43 (20.6%) as mild GIB: 28 (13.5%) on VKA, and 15 (7.2%) on DOAC. We did not find significant differences between VKA and DOAC groups. Interestingly, in patients with severe CKD, there was a higher percentage of major GIB in the VKA group when compared to the DOAC group (16% *vs*. 4.5%, p=0.030), with no differences in severe or mild GIB. In this VKA subgroup, a 41% of patients presented with INR values over therapeutic range on admission. We did not find differences between AVK and DOAC groups in patients with moderate CKD or in those with no CKD.

Clinical characteristics of severe GIB are described in **table 3**. All patients on VKA were taking acenocoumarin. DOAC treatment distribution was as follows: seven (58.3%) patients were taking rivaroxaban, four (33.3%) apixaban and one (8.4%), dabigatran. Location of severe bleeding was different between groups, with a higher, although no significant, incidence of upper GIB in patients receiving VKA (52.6 % *vs.* 25 %, p= 0.12), while patients treated with DOAC had higher incidence of lower GIB (75% *vs.* 36.8%, p= 0.03). We also found differences in the aetiology of severe GIB, although they did not reach statistical significance: peptic ulcer disease was the most frequent in patients on VKA (26.5 % *vs*. 8.3%, p= 0.21), while diverticular bleeding was the most frequent in patients on DOAC (33.3% *vs.* 10.5%, p=0.11). Remarkably, angiodysplasia was the second most common cause of severe GIB in both groups, and the single most common aetiology of severe GIB in our series. Only one (5.3%) patient with severe GIB

on VKA died during hospitalization from hospital-acquired pneumonia.

DISCUSSION

Our data show that in real life, in a tertiary referral hospital, severity of GIB is similar in patients under anticoagulation therapy treatment regardless of the type of anticoagulation used (DOAC or VKA).

DOAC therapy has been associated with higher incidence of GIB (4, 5) but information regarding the severity and aetiology of GIB in real life patients receiving DOAC compared to VKA is scarce. Most available data derive from observational cohorts or retrospective studies (6-10), although a recent study has prospectively compared clinical outcomes in patients receiving DOAC *vs.* VKA, but only in patients presenting with upper GIB (11). We included patients presenting to the ED with GIB, both upper and lower, and this population mainly consisted of elderly patients, frequently suffering from cardiovascular comorbidities, and mostly receiving anticoagulation for NVAF. The mean age of our patients was similar to patients on DOAC in a real-life study performed in Spain (12), although that study was designed to compare the incidence of major bleeding events between DOAC and VKA and not severity, but also to other recently published real-life studies of GIB in patients under anticoagulation comparing clinical and endoscopic features, aetiology and severity (6,10,11). Comparing comorbidities, we found a higher prevalence of severe CKD in patients on VKA, and higher prevalence of pre-existing cerebrovascular disease in patients on DOAC, probably as a consequence of actual recommendations in clinical practice (13-14).

Regarding the source of bleeding, lower GIB was the most common location in both groups, which could be explained by the ageing of the population, and the change in GIB epidemiology observed in the last years (13). However, the use of VKA has been associated with a major incidence of upper GIB, particularly peptic-ulcer disease, and we also found that peptic-ulcer disease was the most common aetiology of GIB in patients on VKA, similarly to previous reports on GIB related to VKA anticoagulation (8,15). In contrast, diverticular disease was the most common source of lower GIB in DOAC patients similarly to data reported in systematic reviews (16). Our results show

that diverticular disease and angiodysplasias were the most common causes of GIB, irrespective of severity, in accordance to previous studies (17). However, it should be pointed out that angiodysplasias are the most common vascular abnormality found in the gastrointestinal tract, and that older age is the most important risk factor for developing angiodysplasias (18).

In terms of severity of the GIB, we did not find significant differences between AVK and DOAC groups. Also, there were no differences on the Hb level on admission, the drop of Hb, the number of PRBC units transfused, and days in hospital, in accordance with a recent observational prospective study in upper GI bleeding (11) and a systematic review (19). These data are in contrast with two retrospective studies in patients with GIB treated with DOAC that show that this group had fewer hospitalizations and required fewer transfusions when compared to VKA (20-21). Interestingly, in patients with severe CKD, we found a higher percentage of major GIB in the AVK group, when compared to DOAC, with no differences in severe or mild GIB in this group. A significant proportion of these patients presented with INR values over therapeutic range on admission, so we cannot exclude that this increase in major GIB was due to their hypercoagulation state, in addition to the CKD-related platelet dysfunction present in these patients. Future prospective multicentre studies will probably help to assess this issue.

Our study has several limitations worth noting that may prevent from stronger conclusions. It is a single centre observational study, with a small number of subjects included. Another important limitation is that we only included patients from the ED that required hospitalization, and therefore, minor bleeding events are missing. Furthermore, we did not follow-up patients after discharge, hence, details on early complications, re-bleeding or early death are lacking. Also, Hb on admission may not clearly reflect the severity of the GIB, as later haemodilution after initial resuscitation may further decrease the Hb values.

Still, our investigation has strengths, as we prospectively evaluated differences in GIB severity, aetiology and outcomes in a real-life setting, including new information on a more representative patient population than those of RCTs, as we only included patients with GIB, and provided information on specific populations usually excluded

from RCTs, such as elderly patients, or patients with history of CKD or cerebrovascular disease. Also, patients on VKA were mostly receiving acenocoumarin which is the most widely used VKA in Spain, instead of warfarin, from which most of the available evidence on the efficacy and safety of VKAs has been derived.

In conclusion, our data suggest that severity and clinical outcomes are similar between patients on DOAC and patients on VKA, regardless of aetiology of GIB. Despite the limitations, our study reflects the routine clinical practice in a tertiary referral hospital. However, future studies in larger cohorts may confirm our data.

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Table 1: Demographic characteristics

	All	**VKA**	**DOAC**	**p**
	n=208	n=119	n=89	
Age (y), mean±SD	79.2±0.8	78.6±0.9	80.2±0.7	0.88
Sex, female, n (%)	118 (56.7)	60.6 (55.0)	52 (59.1)	0.33
Hypertension, n (%)	189 (90.9)	109 (90.8)	80 (90.9)	0.59
Diabetes mellitus, n (%)	69 (33.2)	40 (33.3)	29 (33)	0.53
Cerebrovascular disease, n (%)	32 (15.4)	12 (10.0)	20 (32.7)	**0.024**
TIA	19 (9.1)	8 (6.7)	11 (12.5)	0.16
Ischemic	12 (5.8)	4 (3.3)	8 (9.1)	0.08
Haemorrhagic	1 (0.5)	0 (0)	1 (1.1)	0.24
CKD				
GFR< 30 mL/min, n (%)	26 (12.5)	20 (17)	6 (6.5)	**0.023**
GFR 30-59 mL/min, n (%)	72 (34.6)	35 (29.4)	37 (41.5)	0.068
GFR > 60 mL/min, n (%)	110 (52.8)	64 (53.7)	46 (55)	0.093
Oncologic disease n (%)	51 (24.5)	25 (20.8)	26 (29.5)	0.28
Active treatment	27 (13.0)	13 (10.8)	11 (12.5)	0.74
Non-Active	24 (11.5)	12 (10.0)	15 (17.0)	0.15
Valvular heart disease n (%)	66 (31.7)	51 (42.5)	15 (17.0)	**0.001**
Mitral stenosis	4 (1.9)	4 (3.3)	0 (0)	0.07
Mechanical valve	25 (12)	25 (20.8)	0 (0)	**0.001**
Biologic valve	5(2.4)	3 (2.5)	2 (2.3)	0.89

Others	32 (15.4)	19 (15.8)	13 (14.8)	0.78
Indication for treatment, n (%)				
Non-valvular atrial fibrillation	160 (76.9)	75 (63)	85 (95.6)	**0.001**
Thrombophilia	18 (8.7)	16 (13.3)	2 (2.2)	**0.007**
Cancer related thrombosis	3 (1.4)	1 (0.8)	2 (2.2)	0.40
Mechanical valve	27 (13.0)	27 (22.5)	0 (0)	**0.001**
Anticoagulants, n (%)				
Acenocoumarin	112 (54.3)	112 (94.1)		
Warfarin	7 (3.4)	7 (5.9)		
Dabigatran	19 (9.2)		19 (21.3)	
Rivaroxaban	29 (13.9)		29 (32.5)	
Apixaban	35 (16.8)		36 (40.4)	
Edoxaban	5 (2.4)		5 (5.8)	
Other Medications, n (%)				
AAS	39 (18.8)	17 (14.3)	21 (23.6)	0.08
Clopidrogrel	11 (5.3)	3 (2.5)	8 (8.9)	0.06
AAS + Clopidogrel	8 (3.8)	3 (2.5)	6 (6.7)	0.13
SSRIs	38 (18.3)	20 (16.7)	18 (20.5)	0.30
Amiodarone	16 (7.7)	5 (4.2)	11 (12.5)	**0.020**
Digoxin	25 (12.0)	18 (15.0)	7 (8.0)	0.09
Statins	103 (49.5)	55 (45.8)	48 (54.5)	0.13
ARB/ACE inhibitor	117 (56.3)	67 (55.8)	50 (56.8)	0.50

AAS, aspirin; **ACE,** angiotensin converting enzyme; **ARB,** angiotensin receptor blocker; **CKD**: chronic kidney disease; **DOAC,** direct oral anticoagulants; GFR: glomerular filtration rate; **SD,** standard deviation; **SSRI**, selective serotonin reuptake inhibitor; **TIA,** transient ischemic attack; **VKA,** vitamin K antagonists; **y,** years.

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Table 2: Location and aetiology of GIB.

	All	**VKA**	**DOAC**	**p**
	n=208	n=119	n=89	
Upper GIB, n (%)	**74 (35.6)**	**44 (37.0)**	**30 (33.8)**	0.62
Mallory-Weiss, n (%)	4 (1.9)	3 (2.5)	1 (1.1)	0.46
Portal hypertension, n (%)	5 (2.4)	2 (1.7)	3 (3.4)	0.43
Ulcer-Peptic disease n (%)	36 (17.3)	24 (20.2)	12 (13.6)	0.20
Angiodysplasia, n (%)	16 (7.8)	10 (8.4)	6 (6.7)	0.65
Tumours, n (%)	8 (3.8)	3 (2.5)	5 (5.6)	0.25
Post-endoscopic procedure, n (%)	5 (2.4)	2 (1.7)	3 (3.4)	0.43
Lower GIB, n (%)	**110 (52.9)**	**61 (51.2)**	**49 (55.0)**	0.58
Diverticular bleeding, n (%)	39 (18.8)	17 (14.3)	22 (24.8)	0.056
Angiodysplasia, n (%)	21 (10.1)	10 (8.4)	11 (12.4)	0.34
Colon cancer, n (%)	10 (4.8)	8 (6.7)	2 (2.2)	0.13
Post-polypectomy bleeding, n (%)	17 (8.2)	11 (9.2)	6 (6.7)	0.51
Actinic proctitis, n (%)	5 (2.4)	4 (3.4)	1 (1.1)	0.29
Rectal ulcer, n (%)	4 (1.9)	2 (1.7)	2 (2.2)	0.76
Hemorrhoids, n (%)	14 (6.7)	9 (7.6)	5 (5.6)	0.57
Obscure GIB, n (%)	**24 (11.5)**	**14 (11.8)**	**10 (11.2)**	0.90

DOAC direct oral anticoagulants; **GIB** Gastrointestinal bleeding; **VKA** vitamin K antagonists.

Table 3: Severe GIB.

	All	**VKA**	**DOAC***	**p**
Severe GIB	n=31	n=19	n=12	
Location				
Upper GIB	13 (41.9%)	10 (52.7%)	3 (25.0%)	0.12
Lower GIB	16 (51.7%)	7 (36.8%)	9 (75.0%)	**0.03**
Obscure GIB	2 (6.4%)	2 (10.5%)	0	0.24
Most common aetiologies				
Acid-peptic disease	6 (19.3%)	5 (26.3%)	1 (8.3%)	0.21
Diverticular	6 (19.3%)	2 (10.5%)	4 (33.3%)	0.11
Angiodysplasia	4 (12.9%)	3 (15.8%)	1 (8.3%)	0.7
Colonic angiodysplasia	3 (9.6%)	1 (5.3%)	2 (16.7%)	0.29
Outcomes				
PRBC transfused	3.93 ± 2.16	4.16 ± 1.84	3.75 ± 6.30	0.41
In-hospital stay	13 ± 6.8	13 ± 7.0	13.2 ± 6.3	0.52

GIB Gastrointestinal bleeding; **PRBC** packed red blood cells; **DOAC** Direct oral anticoagulants; **VKA** Vitamin K antagonists

*DOAC Group: 7 rivaroxaban, 4 apixaban 1 dabigatran.

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Figure legends

Figure 1: Flowchart of included patients.