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Clinical and endoscopic features of severe acute gastrointestinal bleeding in elderly patients treated with direct oral anticoagulants: a multicentre study

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Abstract

Background: The aim of the study was to describe the clinical and endoscopic characteristics and management of severe acute gastrointestinal (GI) bleeding in patients treated with direct oral anticoagulants (DOACs).

Methods: Patients hospitalized for severe GI bleeding under DOAC therapy were identified in 36 centres between June 2013 and March 2016. Clinical outcomes including re-bleeding, major cerebral and cardiovascular events or all-cause mortality were assessed initially and 30 days after admission.

Results: A total of 59 patients with anonymized detailed endoscopy reports for severe GI bleeding were considered. Mean age was 79.3 ± 10.0 years and 61.3% of patients were men. Patients had histories of hypertension (65.6%), heart failure (29.5%), coronary artery disease (27.9%), stroke (19.7%) and peripheral vascular disease (36.1%). Life-threatening bleeding was observed in 42.6%. Mean number of packed red blood cells transfused was 3.4 (range 1–31). Aetiology of bleeding (identified in 66.2% of cases) was peptic gastroduodenal ulcers (22%), diverticula (11.9%), angiodysplasia (8.5%), colorectal neoplasia (5.1%) and anorectal causes (5.1%). Endoscopic haemostasis was performed in 37.7% of patients. A low haemoglobin level was predictive of life-threatening bleeding and death in multivariate analysis. All-cause mortality rate at day 30 was 11.8%.

Conclusions: In this cohort of elderly patients with multiple comorbidities treated with DOACs, the main cause of severe acute GI bleeding was peptic gastroduodenal ulcer and mortality was high.

Keywords: apixaban, dabigatran, direct oral anticoagulants, endoscopy, gastrointestinal bleeding, haemostasis, rivaroxaban

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Introduction

Direct oral anticoagulants (DOACs) have been used for almost a decade as an alternative to vitamin K agonists (VKAs) in preventing stroke in nonvalvular atrial fibrillation (NVAF), and for management of deep vein thrombosis (DVT) and pulmonary embolism (PE) with similar or higher efficacy and decrease in overall bleeding risk.[1,2] DOACs have a common rapid onset of action, between 30 min and 4 h, and are administered in a fixed dose without the need for drug monitoring or dose adjustment except for renal impairment.[3] Nowadays DOACs represent an important part of new oral anticoagulant drug prescriptions with growing cardiovascular indications. If the patient is eligible, prescription of a DOAC is now recommended in preference to a VKA in the NVAF setting, and is an option in very specific cases of

valvular AF.[4,5] They might also be used as a maintenance antithrombotic strategy after ST-elevation myocardial infarction in patients with low bleeding risk.[6] Dabigatran (a direct thrombin inhibitor), rivaroxaban and apixaban (direct factor Xa inhibitors) are currently the main DOACs used in Europe.

A meta-analysis of the first four pivotal phase III clinical trials for embolic events prevention in NVAF showed a 25% increase of gastrointestinal (GI) bleeding risk in patients treated with DOACs.[1] Other meta-analyses and analyses of individual randomized controlled trials (RCTs) in NVAF and DVT/PE seemed to suggest the same increase in this risk but without reaching statistical significance.[7,8] However, most recent studies tend to contradict these findings indicating that DOACs could be as safe or even show a lower risk of GI bleeding than VKAs.[9–11] According to most of these meta-analyses of RCTs and real-life observational studies, apixaban seems to be associated with a minimal risk of all-cause bleeding, and more particularly intracranial and GI bleeding.[2,12–14]

Description of GI bleeding characteristics, management and prognosis under DOAC therapy remains scarce. The Dresden novel oral anticoagulant (NOAC) registry recently reported some real-life data from 143 cases of GI bleeding under DOAC therapy compared with historical cohorts of GI bleeding under VKAs (185 cases) or antiplatelet drugs (711 cases).[15] To our knowledge, studies from this registry are the only prospective data on endoscopic descriptions of bleeding cause and management of acute GI bleeding to have been reported in patients treated with DOACs. The main objective of this study was to describe in more detail the clinical and endoscopic features as well as management strategies, including endoscopic haemostasis, of acute severe GI bleeding in patients treated with DOACs included in a prospective multicentre registry.

Materials and methods

The Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux (GIHP-NACO) registry (NCT02185027) is a prospective, multicentre registry, set up by the Groupe d'Intérêt en Hémostase Péri-opératoire. It records patients treated with DOACs (i.e. dabigatran, rivaroxaban or apixaban) and hospitalized for spontaneous or post-traumatic bleeding, but also patients in need of urgent invasive procedures. Spontaneous bleeding is defined as a bleeding event not related to an external cause (either traumatic or iatrogenic). In this registry, patients were enrolled in 36 centres in university ($n = 26$), general ($n = 7$) and private hospitals ($n = 3$) in France and Belgium. The registry opened in June 2013 and closed for inclusion in March 2016. Hospitalized patients presenting with bleeding events were screened by local investigators in each centre. Data including demographic, clinical, laboratory tests and treatment were collected prospectively by using an electronic case report form. The use of transfused units of packed red blood cells (RBC), platelets, frozen plasma transfusions and procoagulant drugs, such as activated or unactivated prothrombin complex concentrates (aPCC/PCC), was assessed.[16,17]

For this study, specific data on endoscopy were obtained retrospectively because they were not part of the initial GIHP-NACO registry case report form. Local investigators from all centres were contacted and asked to provide detailed anonymized endoscopy reports. Endoscopic features and management of bleeding were described by presenting symptom (e.g. haematemesis, melena, rectal bleeding), type of endoscopy performed (e.g. gastroscopy, colonoscopy, flexible sigmoidoscopy, capsule endoscopy), time between admission and first endoscopy, diagnostic performance of endoscopy (defined as identification of the cause of bleeding during the procedure), bleeding cause, need for therapeutic endoscopy and need for repeated endoscopies.

The GIHP-NACO registry was approved by the institutional review board (Comité d'Ethique des Centres d'Investigation Clinique de l'Inter-région Rhône-Alpes-Auvergne, France; institutional review board number 5891, reference 013-02). Oral consent was obtained from all patients or proxies. Written consent of the patients was not necessary according to French law regarding observational studies. This study was supported by the GIHP-NACO and no extra funding was needed.

Clinical outcome definitions

Clinical outcomes such as major cerebral and cardiovascular events (MACCEs), re-bleeding or

all-cause mortality were assessed initially and at 30 days after admission.

MACCEs were defined as cardiovascular complication events with potentially fatal outcome as follows: acute coronary syndrome; stroke or transient ischaemic attack; systemic embolism; deep venous thrombosis or pulmonary embolism; pulmonary oedema; cardiogenic shock.

Bleeding events were classified as life threatening or not according to the overall clinical status (i.e. vital signs, laboratory values, transfusion need) assessed by the treating physician in each centre.

Major bleeding was defined according to the International Society of Thrombosis and Haemostasis criteria as an overt bleeding with fatal bleeding and/or bleeding causing a fall in haemoglobin level of 20 g/L or more, or leading to transfusion of two or more units of whole blood or RBC.[18]

Statistical analysis

Continuous parameters were reported as mean +/− standard deviation, and discrete parameters were reported as numbers and percentage (%). Group comparisons were made with independent-samples *t* tests for continuous data and Pearson's chi-square tests for categorical data. Multivariable logistic regression was used to test eligible prognostic factors for two outcomes, life-threatening bleeding and 30-day all-cause mortality. Results were considered statistically significant for *p* values under 0.05. Statistical analysis was performed using IBM® SPSS® Statistics 22.0 (Armonk, New York, USA).

Results

Patients' characteristics

A total of 732 patients presenting with severe bleeding under DOAC therapy and admitted to 36 hospitals were included in the GIHP-NACO registry. Of these 732 patients, 580 (79%) presented with spontaneous bleeding. GI bleeding was reported in 211 patients, representing 37% of spontaneous bleeding events.

A total of 166 patients (78.7%) were admitted to hospital from the emergency room, and 35 (16.6%) and 10 (4.7%) directly to intensive care units or interventional departments (operating room, endoscopy room, radiology department) through emergency medical services.

We analysed 59 patients with GI bleeding who had detailed anonymized endoscopy reports. There was no significant statistical difference regarding demographic and clinical characteristics compared with the overall GI bleeding population (Table 1).

The demographic and clinical characteristics of patients with GI bleeding are presented in Table 1. In our study population, 24 patients (38.7%) were treated with dabigatran, 36 (58.1%) with rivaroxaban and 2 (3.2%) with apixaban. Some patients received antiplatelet drugs associated with their anticoagulant therapy: 22.3% aspirin and 1.4% clopidogrel. Men represented 61.3% of the population. Patients were older than 75 years in 65.9% of cases and 80.7% presented with moderate to severe renal failure at admission. Mean creatinine clearance was 43.05 ± 1.7 ml/min. A total of 57 of patients (91.9%) were treated for NVAF and 5 (8.1%) for venous thromboembolism (VTE). Time between first treatment with a DOAC and GI bleeding was less than 6 months for 34.5% of patients.

GI bleeding severity and clinical management

Severity and clinical bleeding management are described in Tables 2 and 3. A life-threatening bleeding was observed in 42.6% of cases, with haemoglobin levels less than 70 g/L for 12 patients (20.3%), and 100 g/L for 40 patients (67.8%). A total of 45 patients (73.8%) required transfusion and 12 (21.3%) required administration of procoagulant drugs. Around 91% of transfused patients needed more than two packed RBC units. The mean number of packed RBC transfused was 3.42 (range 1–31).

Endoscopic features and bleeding management

The first endoscopy procedure was performed within the first 24 h for 40.6% of patients, and between 24 h and 48 h for 47.5% of patients.

Patients with GI bleeding presented with haematemesis in 11.9% of cases (associated with melena in two patients), melena in 53.2% and rectal bleeding in 50.8% (associated with melena in five patients). Gastroscopy was performed in 77.3%

Table 1. Demographic and clinical characteristics.

	Study population ($n = 59$)	**GIHP-NACO GI bleeding population ($n = 211$)**
Mean age (years)	79.3 ± 10	78.4 ± 10
Sex % female	24 (38.7)	93 (44.1)
Medical history (%)		
Hypertension	40 (65.6)	130 (63.1)
Heart failure or reduced LVEF	18 (29.5)	46 (22.3)
Coronary artery disease	17 (27.9)	44 (21.4)
Stroke	12 (19.7)	53 (25.7)
Diabetes mellitus	13 (21.3)	42 (20.4)
Peripheral vascular disease	22 (36.1)	60 (29.1)
Liver disease	7 (11.5)	16 (7.8)
Alcohol abuse	10 (16.4)	21 (10.2)
Bleeding	13 (21.3)	41 (20.0)
Labile INR under previous VKA therapy	3 (5.0)	21 (10.3)
Creatinine clearance		
Cockcroft–Gault, ml/min (%)		
> 60	11 (19.3)	36 (19)
30–59	27 (47.4)	103 (54)
15–29	18 (31.6)	46 (24)
< 15	1 (1.8)	7 (4)
Indication		
Patients with NVAF, *n* (%)	57 (91.9)	182 (86)
Patients with VTE, *n* (%)	5 (8.1)	21 (10)
Indication unknown (%)	0 (0.0)	4 (2)
Off-label indication (%)	0 (0.0)	4 (2)
Anticoagulant regimen *n* (%)		
Dabigatran	24 (38.7)	80 (37.9)
110 mg BID	18 (75.0)	58 (27.5)
150 mg BID	5 (20.8)	16 (7.6)
Other or unknown	1 (4.2)	137 (64.9)

Table 1. (Continued)

	Study population ($n = 59$)	**GIHP-NACO GI bleeding population ($n = 211$)**
Rivaroxaban	36 (58.1)	114 (54.0)
20 mg OD	17 (48.6)	58 (27.5)
15 mg OD	17 (48.6)	45 (21.3)
15 mg BID	–	2 (0.9)
Other or unknown	1 (2.9)	106 (50.3)
Apixaban	2 (3.2)	17 (8.1)
2.5 mg BID	1 (50.0)	10 (4.7)
5 mg BID	1 (50.0)	7 (3.3)
Other or unknown	–	194 (92.0)
Time between first treatment and bleeding (%)		
$<$ 1 week	1 (1.6)	9 (4.3)
1 week to 1 month	8 (13.1)	26 (12.5)
1–6 months	12 (19.7)	42 (20.2)
$>$ 6 months	21 (34.4)	82 (39.4)
Unknown	19 (31.1)	49 (23.6)

No significant statistical difference was shown between the overall population and patients with an available emergency endoscopy report. BID, twice a day; GI, gastrointestinal; GIHP-NACO, Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux; INR, international normalized ratio; LVEF, left ventricular ejection fraction; NVAF, nonvalvular atrial fibrillation; OD, once a day; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 2. Severity of bleeding.

	Study population ($n = 59$)	**GIHP-NACO GI bleeding population ($n = 211$)**
Life-threatening bleeding, n **(%)**	26 (42.6)	87 (41.4)
Haemoglobin at admission, g/L, mean	90 ± 30	90 ± 30
Transfusion burden		
$<$ 2 packed RBC units	4 (9.1)	8 (5.8)
$\geqslant$ 2 packed RBC units	40 (90.9)	129 (94.2)
$\geqslant$ 4 packed RBC units	15 (34.1)	47 (34.3)
Massive transfusion of $\geqslant$ 10 packed RBC	1 (2.3)	4 (2.9)

No significant statistical difference was shown between the overall population and patients with an available emergency endoscopy report. GI, gastrointestinal; GIHP-NACO, Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux; RBC, red blood cells.

Table 3. Bleeding management.

	Study population ($n = 59$)	GIHP-NACO GI bleeding population ($n = 211$)
Transfusion, n **(%)**	45 (73.8)	140 (70.0)
Packed RBC units, *n* (%)	44 (71.0)	138 (65.4)
Platelets units, *n* (%)	4 (6.5)	10 (4.7)
Fresh frozen plasma units, *n* (%)	10 (16.1)	33 (15.6)
Fibrinogen concentrate units, *n* (%)	1 (1.6)	1 (0.5)
Procoagulant drugs, n **(%)**	13 (21.3)	66 (33)
PCC, *n* (%)	10 (83.3)	56 (87.5)
aPCC, *n* (%)	2 (15.4)	8 (12.3)
Mechanical means (%) (compression, gauze packing)	17 (27.9)	47 (23.6)
Intervention for haemostasis control (%)	23 (37.7)	61 (30.5)
Endoscopy (%)	20 (87.0)	47 (77.0)
Surgery (%)	3 (13.0)	8 (13.1)
Embolization (%)	–	5 (8.2)

No significant statistical difference was shown between the overall population and patients with an available emergency endoscopy report. aPPC, activated prothrombin complex concentrate; GI, gastrointestinal; GIHP-NACO, Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux; PCC, prothrombin complex concentrate; RBC, red blood cells.

of patients and 54.8% also underwent colonoscopy or flexible sigmoidoscopy.

Upper GI bleeding was characterized in 40.7% and lower GI bleeding in 35.6%. Bleeding location was not clearly identified in 23.7% (14/59) of patients despite endoscopy (including capsule endoscopy in two cases).

GI bleeding cause was identified using endoscopy in 66.2% of cases and in 35% by gastroscopy alone. Bleeding causes were distributed as follows: 22% (13/59) from peptic gastroduodenal ulcers or erosions; 11.9% (7/59) from diverticula; 8.5% (5/59) from angiodysplasia; 5.1% (3/59) from colorectal neoplasia; 5.1% (3/59) from benign anorectal causes; 3.4% (2/59) related to portal hypertension (one patient with four GOV1 varices and another with portal hypertensive gastropathy); 10.2% from other causes including one case of colitis, two oesophagitis and two Dieulafoy's ulcers.

Intervention for haemostasis control was needed for 37.7% of patients, while 16.0% showed active bleeding during endoscopy. When haemostasis was performed endoscopically, 61.5% of patients received epinephrine injection therapy, 15.4% had clips, 15.4% argon plasma coagulation, 4% band ligation and 4% haemostatic powder spray. Out of the four patients treated for peptic ulcer bleeding, two (50%) had a combined therapy of epinephrine injection and clipping. Around 5% of patients underwent a second endoscopy for short-term bleeding recurrence.

30-day outcomes and prognosis

MACCEs were observed in 11.9% of patients. Re-bleeding occurred in seven patients (11.9%). A total of 23 patients (11.8%) died within 30 days, all of them during hospitalization. Cause of death was established as bleeding or re-bleeding at the same origin or a new location in 34.8% of cases (Table 4).

Table 4. 30-day outcomes.

	Study population ($n = 59$)	GIHP-NACO GI bleeding population ($n = 211$)
MACCE, n **(%)**	10 (16.9)	23 (11.9)
Venous thromboembolism, *n* (%)	–	2 (9.5)
Ischaemic stroke, *n* (%)	–	1 (4.5)
Systemic emboli, *n* (%)	1 (10.0)	2 (9.5)
Acute coronary syndrome, *n* (%)	1 (10.0)	5 (23.8)
Pulmonary oedema, *n* (%)	6 (60.0)	8 (38.1)
Cardiogenic shock, *n* (%)	1 (10.0)	4 (18.2)
All-cause mortality, n **(%)**	8 (12.9)	23 (11.8)
Mortality during hospitalization, *n* (%)	8 (100)	23 (100)
Cause of death, n **(%)**		
Neurological/CNS	1 (12.5)	2 (8.7)
Bleeding	4 (50.0)	8 (34.8)
Cardiac	1 (12.5)	6 (26.1)
Sepsis	–	1 (4.3)
Other or undetermined	2 (25.0)	6 (26.1)

No significant statistical difference was shown between the overall population and patients with available emergency endoscopy report. CNS, central nervous system; GI, gastrointestinal; GIHP-NACO, Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux; MACCE, major cerebral and cardiovascular events.

Univariate analysis. Haemoglobin levels were significantly lower when the bleeding was considered life threatening (73 g/L) compared with non-life-threatening situations (102 g/L) [difference −29.1, 95% confidence interval (CI) −36.9 to −21.4, $p < 0.001$]. Age was significantly higher in life-threatening situations (80.6 years old) compared with non-life-threatening situations (76.9 years old) (difference 3.72, 95% CI 0.98–6.45, $p = 0.008$). Creatinine clearance was significantly lower when the bleeding was considered life threatening (36.4 ml/min) compared with non-life-threatening situations (47.2 ml/min) (difference −10.75, 95% CI −17.47 to −4.02, $p = 0.002$). Haemoglobin levels, age and creatinine clearance were not significantly different according to mortality status. The number of packed RBC units transfused was not significantly different according to the life-threatening or mortality status. Patients presenting with melena had significantly more life-threatening bleedings ($p = 0.041$). There was no difference in life-threatening bleeding or all-cause mortality when considering the cause of the bleeding. There was no difference between DOACs in life-threatening bleeding or all-cause mortality, except for apixaban, which had a significantly lower representation in life-threatening situations ($p = 0.038$), but no difference in mortality.

Multivariate analysis. A low haemoglobin level was the only predictive factor for life-threatening bleeding ($p < 0.001$) and all-cause mortality ($p = 0.016$) in the multivariate analysis.

Discussion

DOACs decrease overall major bleeding events when compared with VKAs, but some studies suggest that the risk of GI bleeding related to

DOACs could be increased. Despite the large use of DOACs, characteristics of GI bleeding and its management are still poorly described. This study described real-life aspects and endoscopic findings in patients with acute severe GI bleeding treated with DOACs.

GI bleeding was the main cause of spontaneous bleeding events in the GIHP-NACO registry, representing more than one third of patients. An analysis of the pivotal RCTs of patients treated with DOACs support this finding with GI bleeding representing 47% mean of all major bleeding events.[19] Studies published by the French pharmacovigilance database (FPVD), the ORANGE study from the UK, the Dutch subset of the European XANTUS registry and the international START-Event registry showed similar data with GI bleeding representing 37%, 44%, 36.8% and 35.9%, respectively, of all bleeding events under DOAC therapy.[20–23]

The relatively low number of 211 GI bleeding events occurring in a 3-year study conducted in more than 30 centres is mainly explained by the fact that we could not capture all consecutive GI bleeding events. Indeed, patients were included at the local physician's discretion.

Our study population was mainly represented by elderly patients (mean age 79.3 ± 10 years) with numerous and important comorbidities, and especially with a history of vascular diseases, mainly receiving DOACs for NVAF. These findings are consistent with the target population for DOAC therapy and with results observed in other cohorts of GI bleeding events under DOACs. Median age was 77 years for patients from the Dresden registry and 79 years in a recent study published by Sengupta and colleagues.[15,24] It is also very similar to patients' demographic characteristics of cohorts and pivotal RCTs of DOACs in NVAF, while for RCTs of DOACs in VTE, patients were younger (55 years).[21,22,25,26]

Most of our patients had renal insufficiency upon admission, most of them with severe decline in renal filtration function. A high prevalence of renal impairment was also found in the global GIHP-NACO cohort, where 69% of patients had moderate to severe renal impairment.[17] This is higher than has been described in other cohorts of GI bleeding. Impaired renal function was observed in only 18% of patients from the Dresden registry and 35% from the XANTUS registry.[21,27] Decline in renal filtration function seems to be more frequent in patients treated for NVAF (58% in the ARISTOTLE trial) compared with those treated for VTE (36% in the AMPLIFY trial and in the EINSTEIN-PE trial).[28–30] This must be interpreted carefully, as the explanation is probably multifactorial, including severe vascular comorbidities and/or acute kidney injury related to bleeding-induced hypovolaemia but true misuse of DOACs in patients with impaired renal function could also be implicated.

Rivaroxaban was the most prescribed DOAC in our study with a DOAC repartition considered representative of what was observed at the time in France as previously described in the FPVD. The FPVD is a mandatory record of all notifications of adverse drug reaction in France. Rivaroxaban, dabigatran and apixaban represented respectively, 59.3%, 37.9% and 2.8% of all 11,366 bleeding notifications in patients treated with DOACs during a 6.3-year period (2009–2015).[20] It is also consistent with what was recently described in the UK over a 3-year period, with 67% of 421 DOAC-related bleeding occurring under rivaroxaban.[23] This distribution is however different from the other cohorts of GI bleeding under DOAC therapy, which showed a more frequent use of dabigatran (37.9% in our cohort, compared with 9.1% and 27.4% in the Dresden registry and the START-Event registry, respectively) and less frequent use of apixaban (8.1% in our cohort, compared with 12.6% and 27.4% in the Dresden registry and the START-Event registry, respectively).[15,22] The relatively low proportion of patients treated with apixaban in this study, while it seems to be the safest DOAC option to prevent GI bleeding, can be explained by its later market approval in France (2013).

In our cohort, the upper GI tract represented the main bleeding location (40.7%) with peptic gastroduodenal ulcer as the first aetiology accounting for almost one quarter of all GI bleeding events. This result is similar to data from the Erlangen cohort in Germany with mostly upper GI bleeding (69.6%).[25] However, it is different from other studies which showed a tendency for an increased rate of lower GI bleeding in patients treated with DOACs. In the Dresden registry, proportions of upper and lower GI location were almost equivalent (respectively, 44.1 and 42.0%). Sengupta and colleagues described 42.6% of

lower GI bleeding (mostly of diverticular origin, 27%) and only 26.9% from the upper GI tract (mostly gastroduodenal ulcers, 15%).[24] Other cohorts and the ROCKET-AF trial also reported a higher proportion of lower GI bleeding, representing more than 50% of GI bleeding under DOACs. Interestingly, these studies showed that the majority of lower GI bleeding causes were from rectal or anal origin (33.3% of haemorrhoid bleeding in the Dresden registry, 41% of anorectal bleeding in an American retrospective cohort and 30% of rectal bleeding in the ARISTOTLE trial).[15,26,28,31–35] In our study, lower GI bleedings were mainly due to diverticular bleeding with only a small proportion of haemorrhoidal bleeding (5.1%). The overrepresentation of upper GI bleeding in our study could be explained by a possible selection bias and the fact that only a quarter of detailed endoscopy reports could be obtained and analysed. Indeed, upper GI bleeding causes could be more likely to induce a severe clinical presentation than lower GI causes and a full endoscopy report.

An endoscopy was performed within the first 24 h for 40.6% of patients, and between 24 h and 48 h for 47.5% of patients, when the anticoagulant effect of DOACs had almost disappeared due to a short onset of action and half-life.[3] It is probably one of the reasons why active bleeding was described during endoscopy in only 16% of cases.

Only about a third of our patients needed endoscopic haemostasis despite a severe initial presentation. Re-bleeding was frequent (11.9%) and much higher than that described by Sengupta and colleagues (3.7% at 90-day follow up in 1338 adults treated with DOACs).[24] This might be partly due to inadequate endoscopic haemostasis. The most common haemostatic therapy was epinephrine injection in more than 50% of cases, sometimes combined with the use of haemostatic clips, with the main bleeding cause being peptic ulcers. Thus, there might be scope for improvement in endoscopic therapy as the European Society of Gastrointestinal Endoscopy now recommends that epinephrine injection should not be used as a monotherapy but always in combination with a second haemostasis modality in management of peptic ulcer bleeding.[36]

The mortality rate in our cohort (11.8% at day 30) was relatively high compared with that described in previous studies. No deaths were reported at day 30 in an American retrospective cohort that included both inpatients and outpatients with a mean haemoglobin level of 112 ± 30 g/L.[26] An in-hospital mortality rate of only 1.6% was observed in the Dresden registry.[15] Most of the pivotal RCTs also showed a mortality rate below 10%.[37,38] This discrepancy could be explained by the fact that our population was a selected cohort of severe acute bleeding episodes compared with most of the previous studies on overall GI bleeding events. Our study is the only one with Sengupta and colleagues to show more than 15% of patients admitted to an intensive care unit. However, no mortality data were available in their study due to a lack of capture by the Marketscan database used.[24]

More than two thirds of our patients needed transfusion of RBC, with a median number of 3.4 units, and more than 15% received fresh frozen plasma. In comparison, only 44.1% (median number of two units), 27.9% and 31% of patients required RBC transfusion in the Dresden registry, the American retrospective cohort and the study by Sengupta and colleagues, respectively.[15,24,26] PCC was administered in around one third of our patients compared with only 4.2% of those from the Dresden registry.[15]

The high proportion of patients treated with dabigatran and showing concomitant moderate to severe renal impairment could also partially explain the high mortality rate in our cohort. Renal excretion of dabigatran is significant (85%) and renal impairment will induce an extension of the drug's half-life and, therefore, a potentially longer and more severe bleeding episode.[3] However, our results are very similar to those described by a French observational study. In a subset of 27 patients presenting with GI bleeding, haemoglobin levels were 78 ± 20 g/L and patients received a mean number of 3.7 RBC units (range 1–15). Of these 27 patients, 3 (11%) died within a 30-day period, all of them from gastroduodenal bleeding with gastroduodenal ulcers being the first bleeding cause (28.6%).[31]

Nevertheless, in our study, with appropriate care only one out of four patients with life-threatening bleeding at admission died within 1 month. A low haemoglobin level was the only predictive factor for life-threatening bleeding and all-cause mortality in our study after adjustment for confounding factors. These results suggest that one of the most important parts of management of GI bleeding in

patients treated with DOACs, in terms of prognosis, might be haemodynamic optimization and transfusion support until the pro-bleeding effect of DOACs disappears. This is consistent with the global improvement in management of GI bleeding in the past few decades, as it is now well known that early intensive resuscitation measures decrease mortality, especially in upper GI bleeding.[39]

According to most of the meta-analyses of RCTs and real-life observational studies, apixaban seems to be associated with a minimal risk of all-cause bleeding, and more particularly intracranial and GI bleeding.[2,12–14] In our cohort, patients treated with apixaban had significantly fewer life-threatening bleeding events than with the other DOACs.

This study has a few limitations related to its observational nature. We cannot exclude a selection bias as our population seemed to show a higher severity of GI bleeding compared with previously published data. This could explain the lower rate of lower GI bleeding in our cohort because upper GI causes could be more likely to induce a severe clinical presentation. Extrapolation of our results is therefore restricted to severe GI bleeding events and cannot apply to all digestive bleeding in patients undertaking DOAC therapy.

One of the main limitations is that detailed endoscopy reports where only available for about a quarter of patients with GI bleeding from the GIHP-NACO cohort. This may be due to the retrospective nature of the endoscopic data collection but could also be explained by the fact that in most emergency settings, and especially at night, endoscopy reports are often handwritten and not structured and integrated in the patient's electronic medical record. This raises the question of improving care and quality of studies by optimizing records of emergency procedures in hospital systems. However, the group of patients with endoscopy reports was comparable for clinical and bleeding care characteristics and therefore can be considered representative of our patients.

Specific reversal agents for DOACs have been recently developed. Idarucizumab, a humanized monoclonal antibody fragment, is now authorized worldwide for dabigatran, and andexanet-alfa, a decoy recombinant factor Xa, is currently under review for rivaroxaban, apixaban and edoxaban. These products were not available at the time of inclusion in this study and their effect in real life would be interesting to report.[40–42]

Conclusion

In this cohort, severe GI bleeding occurred in a population of elderly patients with multiple and severe cardiovascular comorbidities and moderate to severe renal impairment. With endoscopy performed within 48 h, most of the bleeding events were observed in the upper GI tract, mainly from gastroduodenal peptic ulcers. The need for endoscopic haemostasis was low compared with the initial clinical severity of the bleeding. While the all-cause mortality rate in our cohort was relatively high (11.8% at day 30), only one out of four patients with life-threatening bleeding at admission died within this period. A low haemoglobin level was the only predictive factor for life-threatening bleeding and all-cause mortality. This study represents one of the largest European cohorts of GI bleeding under DOAC therapy and provides information about endoscopic findings and management in those patients. However, considering the lack of studies focusing on GI bleeding and endoscopic management under DOAC therapy, especially in a context of newly available specific antidotes, more real-life studies are needed to better assess these situations.

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Conflict of interest statement

CB has served as a speaker and a consultant for Bayer Healthcare and Boston Scientific. RB has served as a speaker and a consultant for Bayer Healthcare. PA has served as a speaker and a consultant for Aspen Pharmacare, Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, Novo Nordisk, Pfizer, Portola, Sanofi and Stago. DD, PA and J-MS had no conflict of interest.

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