Reducing upper digestive bleeding risk in patients treated with direct oral anticoagulants and concomitant infection with *Helicobacter pylori*

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Abstract. Direct oral anticoagulants (DOACs) such as apixaban or dabigatran are excellent options in preventing embolic cardiovascular events. Observational studies have shown that gastrointestinal bleeding risks produced by DOACs could be lowered when correcting some host co-factors i.e. *Helicobacter pylori* (HP) infection. The upper digestive bleeding (UDB) rates in patients with DOAC indication and the usefulness of anti-HP therapy addition were compared. An observational retrospective study was conducted of medical records of 260 patients treated with DOACs, 130 of whom were concomitantly treated for HP infection in accordance with Maastricht V/Florence consensus. The severity of bleeding, the complexity of endoscopic treatment required to stop the bleeding, the re-bleeding rates, the surgical treatment indication and the overall mortality rates were compared between the groups. The risk of UDB was higher in HP-untreated patients in both types of DOACs used (respectively 2.08, 2.02). HP-untreated Forrest Ia/Ib/IIa and IIb DOACs patients had more severe bleedings compared with same class of HP-treated patients (P=0.007/0.005; 0.009/0.006; 0.048/0.005, 0.044/0.049, respectively). Endoscopic treatments such as adrenaline injections combined with metallic clip attachments were more frequently mandatory in HP-untreated DOACs patients for classes Ia/b and IIa (respectively, P=0.000/0.001, P=0.003/0.003). The re-bleeding rates were higher in HP-untreated patients with concomitant DOACs (OR 82.5; 95% CI 30.1-121.7; P=0.005). A history of peptic ulcer or UDB was associated with a 2.9-fold higher risk of UDB in HP-untreated compared with HP-treated patients, slightly increased for dabigatran compared with apixaban (RR 3.06, 2.72, P<0.5, respectively). Surgical intervention and the UDB-related mortality rates were higher in HP-untreated patients (P=0.041/0.044, P=0.007, respectively). HP-eradication treatment and bacterial clearance improve the safety profile of DOACs treatment, especially in fragile patients, in whom the UDB rates can be lowered, and the overall outcome can be enhanced by this combined approach.

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Introduction

Direct oral anticoagulants (DOACs) include drugs such as direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) which are the first choice of anticoagulant treatment, being favored over conventional oral anticoagulants i.e. warfarin. DOACs are used both for prevention and treatment of embolic stroke in non-valvular atrial fibrillation (AF) or in the prevention and treatment of venous thromboembolism (VTE). Arguments favoring the use of DOACs combine their bioavailability, the facile administration, and the safety profile, based on

meta-analyses of phase IV randomized clinical trials (RTCs). The rapid onset and offset of action and the exclusion of the mandatory therapy-monitoring such as in warfarin use, due to predictable pharmacodynamics, were valuable arguments for DOACs extensive use (1-3). Despite these evidence-based arguments, the risk of upper gastrointestinal (GI) tract bleeding in real-life settings remains a concern, *Helicobacter pylori* (HP) infection being one of the most common risk factors for upper digestive bleeding (UDB) occurrence in patients treated with DOACs. Meta-analyses confirmed the risk of UDB in patients with HP infection treated with DOACs (4).

We aimed to establish whether HP-eradication treatment influences the outcome of patients treated with DOACs admitted to the Cardiology and Gastroenterology Departments of the Emergency Hospital of Constanta, Romania, over a period of two years, and compared the UDB rates in patients on DOACs treatment for different indications, with or without anti-HP treatment.

Patients and methods

An observational retrospective study was performed on patients admitted to the Cardiology and Gastroenterology Departments of Constanta Emergency Hospital, Romania, over a period of three years, under concomitant treatment with one proton pump inhibitor (PPI) and two antibiotics (for HP infection) and DOACs. Usefulness of anti-HP therapy in improving the UDB risk and overall cardiovascular outcome in these patients was evaluated. Medical files of 260 patients under DOACs treatment (dabigatran or apixaban) and with documented HP infection were studied. The study was approved by the Ethics Committee of the Emergency Hospital of Constanta, Romania (no. 37/16.12.2019).

The rate of UDB occurrence was compared together with severity of bleeding according to Forrest classification, response to endoscopic hemostatic treatments, re-bleeding rates, the length of DOAC withdrawal periods needed for UDB management, the length of hospitalization, and the mortality rates in DOAC-treated patients, with or without co-administration of anti-HP treatment. Patients were divided into two groups, according to anti-HP treatment: 130 patients without anti-HP treatment and 130 patients with HP-treatment, and the results were compared for all the above-mentioned features. The enrollment of patients' medical files in the statistical analysis was approved after the documentation of HP infection. Stool antigen (Ag) or urease tests during endoscopy were required as criteria for the diagnosis of HP infection. The triple or quadruple therapy with one proton pump inhibitor (PPI) and two antibiotics (e.g. clarithromycin, amoxicillin, levofloxacin, metronidazole, tinidazole), and occasionally the fourth drug, such as bismuth subcitrate/subsalicilate, were the anti-HP treatment options, the length of treatment being in accordance to Maastricht V/Florence consensus (5). The severity of bleeding was documented. Forrest endoscopy classification, hemostatic endoscopic maneuvers, the DOACs temporary withdrawal period, and the mortality rates were noted. The SPSS soft was used for the statistical analysis of the results. t-test and Pearson correlation coefficients were used for continuous variables analysis and comparations.

Results

Characteristics of the patients. Features, such as age, sex, renal and liver impairments, history of peptic ulcer and UDB, the cardiovascular indication for DOACs, and other ulcerous medications, such as anti-platelet, NSAIDs and aspirin co-administration, associated with the DOACs-related UDB were noted and are summarized in Table I.

Upper digestive bleeding risk factors in HP infected patients treated with DOACs. Age over 75 years was associated with an increased risk of DOACs-related UDB in both patient groups. Among patients receiving dabigatran, there was a 2.08-fold increase in the risk of UDB in HP-untreated group compared with HP-treated group, and among patients receiving apixaban there was a 2.02 risk of UDB of HP-untreated compared with HP treated patients. A higher risk of major UDB was also observed in HP-untreated patients aged over 75 years receiving both DOACs, regardless of formula used. Concomitant antiplatelet therapy associated with DOACs was studied, antiplatelet therapy being a well-recognized risk factor for digestive bleeding (6,7). Regardless of HP presence, among dabigatran users, concomitant antiplatelet use was associated with a 45% higher risk of UDB compared with only a 15% higher risk for apixaban (P=0.003). The highest risk of UDB was seen in patients with acute coronary syndrome HP-untreated, in whom DOACs were co-prescribed along with antiplatelet agents, compared with patients with a similar profile, but HP-treated (RR 2.36 for dabigatran, and RR 2.43 for apixaban). The minimum risk was encountered in venous thromboembolism (VTE) prevention after lower abdominal or orthopedic surgery, still also significantly higher in HP-untreated patients compared with HP-treated patients (RR 1.31 for apixaban, and RR 1.38 for dabigatran). In patients with DOAC prescription for pulmonary embolism, we also found an increased risk of UDB in HP-untreated compared with HP-treated patients (RR 1.57 for dabigatran, and 1.68 for apixaban). Patients with impaired renal function were more likely to have drug accumulation, especially for dabigatran, since clearance of most DOACs depends on renal excretion, and hence higher bleeding risk occurs (8). In our series of patients with impaired renal function, but with Cl cr. higher than 30 ml/min, the risk of UDB was increased in HP-untreated patients compared with HP-treated patients, especially for dabigatran group (RR 1.23 for dabigatran, and RR 1.09 for apixaban). A prior history of peptic ulcer or UDB was associated with a 2.9-fold higher risk of UDB in HP-untreated patients compared with HP-treated patients, slightly increased for anti-factor Xa drugs compared with anti-thrombin drugs (respectively RR 3.06, 2.72, P<0.5, ns) (Table II).

Severity of UDB related to risk factors in patients treated with DOACs. The severity of bleeding and the course and outcome of patients were studied. According to Forrest endoscopic classification, HP-untreated Forrest grade Ia/b, IIa/b DOACs patients had more severe bleedings compared with same classes of HP-treated patients (P=0.007/0.005; 0.009/0.006; 0.048/0.005, 0.044/0.049, respectively) while stages IIc and III did not encounter any differences between the two studied groups (P=0.055/0.058, 0.091/0.077, respectively). The rate of

Table I. Characteristics of patients treated with DOACs with concomitant HP infection.

Risk factors	DOACs in HP-untreated patients N=130 Dabigatran/apixaban	DOACs in HP-treated patients N=130 Dabigatran/apixaban	P-values Dabigatran/apixaban
Sex			
Males	36/30	35/32	0.087
Females	32/32	32/31	0.057
Age, mean (years)	69±7.11	70±9.02	0.067
Renal function			
Cr cl <50 ml/min	12/36	18/19	0.077
Cr cl >50 ml/min	31/51	38/55	0.061
Liver function tests			
Normal LFT	48/42	50/52	0.199
Abnormal LFT	16/14	14/12	0.210
History			
Peptic ulcer	28/22	30/25	0.227
UDB	19/15	17/16	0.099
DOAC indication			
DVT	11/11	10/12	0.087
TE	12/15	13/13	0.173
NVAF	24/20	21/22	0.090
Stroke	9/5	7/4	0.093
ACS	10/12	16/12	0.055

DOAC, direct oral anticoagulant; HP, *Helicobacter pylori*; UDB, upper digestive bleeding.

Table II. The relative risk of UDB in HP-treated compared with HP-untreated patients during DOAC treatment.

	UDB occurrence			
Patients' risk factors	DOAC (D/A) HP-untreated patients (N=130)	DOAC (D/A) HP-treated patients (N=130)	P-values	RR
Age >75 years	18/15	9/8	0.004	2.08/2.02
DOAC indication				
DVT	7/5	4/2	0.022	1.38/1.33
TE	6/5	3/3	0.027	1.57/1.68
NVAF	15/11	7/5	0.037	2.24/2.12
Stroke	7/4	4/2	0.019	1.96/1.88
ACS	8/7	3/3	0.008	2.36/2.43
Renal function Cl cr=30-50 ml/min	8/8	3/4	0.044	1.23/1.09
Peptic ulcer/UDB History	22/18	12/9	0.006	3.07/2.72

DOAC, direct oral anticoagulant; HP, *Helicobacter pylori*; UDB, upper digestive bleeding.

re-bleeding was also studied in DOACs patients. Untreated-HP infection was found to be the only independent risk factor for re-bleeding. In these patients, the rate of re-bleeding was 21.33%, while in HP-treated DOACs patients it was 15%, significantly lower (OR 82.5; 95% CI 30.1-121.7; P=0.005). The need for endoscopy re-intervention was mandatory in more HP-untreated compared with HP-treated DOAC patients in classes I and II regardless of DOACs used (OR 78.9; 95% CI 22-78.6; P=0.003). The hemostatic endoscopic therapy was more complex, using at least two hemostatic maneuvers, i.e. adrenaline injections combined with metallic clip attachments in HP-untreated compared with HP treated DOAC patients in classes Ia/b and IIa (respectively, P=0.000/0.001, P=0.003/0.003). The need for surgical treatment was imperative also in HP-untreated compared with HP-treated DOAC patients in classes Ia and Ib, regardless of the DOAC used

Table III. The severity of UDB in HP-treated compared with HP-untreated DOACs patients.

Severity of bleeding	DOAC (D/A) HP-untreated patients (N=130)	DOAC (D/A) HP-treated patients (N=130)	P-values	RR
Forrest classification				
Ia	10/5	4/3	0.007/0.005	2.99/1.65
Ib	11/5	4/2	0.009/0.006	3.03/2.3
IIa	9/9	5/3	0.044/0.005	2.55/3
IIb	7/6	4/3	0.048/0.049	1.58/2
IIc	4/5	3/3	0.055/0.058	1.2/1.3
III	1/2	2/1	0.091/0.077	0.5/2
Endoscopic hemostatic maneuvers				
Hemoclips	13/10	11/5	0.007/0.006	-
Hemostatic injections	10/8	9/4	0.071/0.055	-
Hemoclips+hemostatic injections	17/15	3/3	0.001/0.003	-
Re-bleeding rates	9/7	3/2	0.003/0.003	3/3.5
DOAC withdrawal period length				
<7 days	25/18	10/8	0.005/0.004	-
7-14 days	13/10	8/4	0.044/0.038	-
>14 days	4/4	2/3	0.068/0.089	-
Surgical treatments	6/4	1/1	0.003/0.022	-
Mortality rate	3.07%	0.76%	0.007	2.01

DOAC, direct oral anticoagulant; HP, *Helicobacter pylori*; UDB, upper digestive bleeding.

(P=0.041, respectively 0.044). The length of withdrawal periods of DOACs caused by UDB was also studied. The length of DOAC withdrawal period usually reflects the severity of bleeding and the time spent for digestive bleeding recovery. In our series, HP-untreated patients required more frequently longer than seven days for DOAC withdrawal than HP-treated patients, especially for Forrest classes Ia/b and IIa (P=0.006). Periods of DOAC withdrawal over fourteen days were similar, regardless of HP treatment concomitance or the type of DOAC used (P=0.077). In terms of mortality, a higher mortality rate was detected in HP-untreated DOAC patients compared with HP-treated DOAC patients (0.007), all of them classified as Forrest Ia and Ib (Table III).

Discussion

Clinical randomized trials have demonstrated that the introduction of DOACs in fragile patients with cardiovascular diseases might improve not only the disease outcome but also the GI bleeding related to conventional ACO treatments. However, the data from real-life settings show the same high risk of GI bleedings (9). Recent meta-analyses actively focused on the GI tract bleeding in patients with cardiovascular diseases treated with anticoagulants, in real-life settings. The DOACs introduction in the clinical practice only partially improved the bleeding rates compared with conventional treatments. The pharmacological characteristics of different DOACs can explain the high rates of GI bleedings. Dabigatran has a half-life ranging between 9 and 17 h, depending on age and renal function. Renal insufficiency with creatinine clearance below 30 ml/min contraindicates its use (8). Dabigatran inhibits the thrombin activity directly, but the inhibition process is reversible. The prodrug is known as dabigatran etexilate. The bioavailability of the prodrug is <7%, the rest being eliminated in the feces. After its absorption in the proximal small bowel, dabigatran etexilate reaches the liver where it is transformed into the active form after its cleavage by the serum and hepatic esterases (10). According to its pharmacokinetics, one can accept that the lower GI bleedings are more frequent with dabigatran, due to its topical effect on the mucosa leading to bleeding, especially on pre-existing gut lesions. On the contrary, warfarin has a high bioavailability, and the topical effect on the GI tract practically does not exist (11). RE-LY trial confirmed the presence of UDB in 47% of patients with dabigatran, indicating that other hemorrhagic mechanisms involving dabigatran use are hypothesized (12).

In our observational study, the percentage of UDB was higher, reaching 61% in dabigatran HP-untreated patients, but only 17% in HP-treated group, with a median of 39% regardless of HP-infection (P=0.0033, 95% CI 12-98.55). On the contrary, apixaban acts by directly inhibiting factor Xa and has a higher rate of bioavailability compared with dabigatran of approx. 50% (13). The half-life of apixaban is around 12 h, and 25% of the absorbed drug is excreted by the kidneys. Renal dysfunction, body weight lower than 60 kg, and age over 80 years decrease the dosage of apixaban, smaller dosages probably positively influencing the GI bleedings rates, especially UDBs. Some observational studies on GI bleedings risks in patients treated with DOACs, when compared with randomized cohort trials (RCTs) (3), reported a lower risk of bleedings due to the

characteristics of cohorts evaluated. While patients recruited for RTCs were older, the majority aged over 80 years, with high risks of secondary cardiovascular events, patients from observational studies had fewer comorbidities, with significantly lower CHA2DS2 scores (congestive heart failure, hypertension, age of 75 years or above, diabetes mellitus, history of stroke, transient ischemic attack or thromboembolism) (4). One major concern about the meta-analysis of observational studies is the bias resulting from the confounding factors. Physicians were preoccupied with the risk factors such as age, the usage of other ulcerous medications and the preexistent upper GI lesions, cardiovascular indication of DOACs and the predictable outcome in such situations, some of them also the presence of HP infection, but less about the potential benefit of its concomitant treatment (14). Our study results raise the hypothesis that concomitant treatment for HP infection in DOAC patients may improve the rate of DOAC-related UDBs and even the cardiovascular outcome, being aware of the prothrombogenic effect associated with HP infection. In our series, the risk of UDB was significantly higher in HP-untreated DOAC patients compared with HP-treated patients, regardless of DOAC used, especially for severe lesions, according to Forrest classification. The relative risk for UDB was the highest in patients treated with dabigatran, estimated at 2.99 compared with apixaban, estimated at 1.65, for Forrest class Ia, but this pattern of UDB occurrence was similar for all Forrest classes, except class III. Our study results showed that among dabigatran users, concomitant antiplatelet treatment was associated with a 45% higher risk of UDB compared with only a 15% higher risk for apixaban (P=0.003, ss). Acute coronary syndrome treated with the association of DOACs and antiplatelet drugs had the highest risks for UDB, regardless of the form of anticoagulant used, but HP-treated patients had fewer UDBs compared with HP-untreated ones. In severe UDBs, the use of specific reversal agents such as andexanet-alfa for apixaban or idarucizumab for dabigatran and urgent endoscopic hemostatic procedures are the standard procedures recommended by the current guidelines (15,16). The complexity of endoscopic hemostatic maneuvers showed that during usage of both DOACs, HP-untreated patients needed more than one hemostatic technique to stop the bleeding. Studies show that the re-bleeding rate of UDB in patients with endoscopic hemostasis ranges from 10 to 30%, regardless of associated host risk factors (17,18). Re-bleeding was also encountered, and our study showed a high risk for all HP-untreated DOACs patients, regardless of the DOACs used or Forrest severity. Various scores such as Rockall and Baylor scores are commonly used to quantify the re-bleeding risk. Still, the Forrest severity classification is the easiest tool to make correlations between the two series examined (19). The re-bleeding rates are different according to Forrest classes, ranging from 5% in class III to 55% in class Ia (18). In our study, the overall rate of re-bleeding was around 18%. DOAC treatments in HP-untreated patients increased the re-bleeding rates to 21.33%, while HP-treatment decreased it to 15%, a value significantly lower (OR 82.5; 95% CI 30.1-121.7; P=0.005). The re-bleeding high rates were responsible for longer DOAC withdrawal to improve digestive hemostasis and more risks for worsening the cardiovascular status and prolonged duration of hospitalization (20). The majority of HP-untreated patients under DOACs therapy needed more than seven days for withdrawal of DOACs. The most severe bleeding (Ia, respectively Ib) required more than 14 days for DOAC withdrawal, regardless of HP treatment. Mandatory surgical intervention is also related to bleedings severity, ranging from 0.5 to 35%, according to Forrest classification (18). In our series, the surgical treatment was significantly more frequent in HP-untreated DOAC patients compared with HP-treated patients, regardless of DOAC type (P=0.003, P=0.022, respectively). The mortality rate in UDB range from 2 to 11%, according to Forrest classification (18). The results of our study showed that the mortality rate in HP-untreated DOAC patients was significantly higher than that of HP-treated DOAC patients (P=0.007, 95% CI 3.3-8.2) and the relative risk was 2.01 times higher in HP-untreated DOAC patients.

HP-eradication treatment and bacterial clearance improve the safety profile of DOAC treatment, especially in fragile cardiovascular patients, in whom the UDB rates can be lowered, and the overall outcome can be enhanced by this combined approach.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the HIPPOCRATE files archive of the Emergency Hospital 'St. Apostle Andrew' of Constanta, (http://www.spitalulconstanta.ro/).

Authors' contributions

AIS, APS, IP, LM, CD, VH and LAT conceived and designed the study; AIS, IP, FV and CD acquired the data; LM, FB, LAT, DOC, FV, SIM, APS and VH analyzed the data; LM, IP, FV, APS, VH and LAT validated the results; VH, FB and LM were responsible for the preparation of the original draft; AIS, LAT, DOC, VH and APS were responsible for the final manuscript editing; AIS, LM, APS, IP, CD and VH supervised the manuscript publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Emergency Hospital of Constanta, Romania (no. 37/16.12.2019).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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