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Emergency admissions for major haemorrhage associated with direct oral anticoagulants

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ABSTRACT

Introduction: To describe the population admitted in an emergency department of a teaching hospital for severe bleeding associated with direct oral anticoagulants (DOAC).
Method: During a three-year period (2012–2014) patients older than 16 years were prospectively identified by haemorrhagic symptoms from computerised requests. At least one of the following criteria defined major haemorrhage: haemorrhagic shock, unstable haemodynamic, need for transfusion or haemostatic procedure, or a life threatening location.
Results: Fifty four patients, 23 receiving dabigatran, 30 rivaroxaban and one apixaban were included, 2 in 2012, 35 in 2013 and 17 in 2014. Median age was 84 years (range 63–99) with a sex ratio of 1.16. Haemorrhagic complications were gastrointestinal (n = 27), intracranial (n = 12) or miscellaneous (n = 15). Indication of DOAC was stroke prevention in atrial fibrillation in 49 cases and deep vein thrombosis in 5 cases. Hospitalization was required for 45 patients (83%) with a mean length of stay of 8.5 days. Sixteen patients needed intensive care. Reversal therapy was prescribed in 11 patients. At 1 month, overall mortality was 24%, reaching 41.7% for intracranial haemorrhage. Among surviving patients, DOAC was stopped in 10 cases, continued in 17 patients and switched for other antithrombotic in 17 patients.
Conclusion: Our study contributes to the post marketing surveillance of major haemorrhagic complications associated with DOAC. It takes part to the knowledge about the course of this severe event in emergencies. Careful awareness in risk benefit assessment, especially in elderly, is needed.

1. Introduction

Direct oral anticoagulants (DOAC) offer several advantages over vitamin K antagonists: more rapid onset of action and shorter half-life, less drug–drug interactions, more predictable pharmacokinetics, and consequently the lack of need for routine haemostatic tests.

Recent international clinical trials have shown that DOACs were non-inferior for stroke prevention in non-valvular atrial fibrillation (AF) with a significant reduction in all-cause mortality compared to warfarin [1]. In this indication, reduction in intracranial haemorrhage has been demonstrated [2] but the risk of gastrointestinal bleeding was slightly increased. In the treatment of venous thromboembolism (VTE), DOACs were as effective and safe than warfarin [3]. All these results have led to the European Medicine Agency approval for dabigatran, rivaroxaban and apixaban in AF patients and more recently for rivaroxaban in the treatment of VTE.

Since market authorization, an increasing number of patients received DOAC with, consequently, patients presenting to emergency department with bleeding complications. Real world data are looked-for to be comforted as regards haemorrhage, keeping in mind concern raised by the absence of available antagonist.

This prospective cohort study focused on patients receiving DOAC and referred to emergency department for severe haemorrhagic event since January 2011. Our objectives were to describe the characteristics of those patients, diagnostic and therapeutic management, and finally 1-month outcome.

2. Material and methods

2.1. Patient selection

The screening, selection and inclusions of patients have been reported previously elsewhere [4]. Briefly, patients older than 16 years admitted in the emergency department of our teaching hospital with direct oral anticoagulants (DOAC) and major haemorrhage were consecutively included between January 1, 2012 and December 31, 2014.

Firstly, haemorrhagic symptoms at emergency admission were screened. Computerised requests based on several related-haemorrhagic diagnostic codes and specific emergency therapies were made every month on electronic health records. Secondly,

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criteria of major bleeding were required. According to the French National Authority for Health (Haute Autorité de Santé — HAS), major bleeding was defined by at least one of the following criteria: haemodynamic instability (systolic arterial pressure < 90 mm Hg or mean arterial pressure < 65 mm Hg), signs of shock, uncontrollable bleeding, need for transfusions of red cell packs, need for haemostatic procedure (embolization, endoscopic procedure, surgery), or a life-threatening bleeding such as intracranial, intra-spinal, intraocular, retroperitoneal, pericardial, thoracic bleeding, compressive muscular haematoma or acute gastrointestinal bleeding. Finally, DOAC was systematically searched for. All direct oral anticoagulants were eligible whatever their indication and their dosage. Patients with intentional overdose with DOAC and patients with multi-trauma were excluded.

For all included patients, the following clinical and biological data were collected from electronic health record: demographics, medical history, treatments with their indication and duration, type of bleeding manifestation, vital signs at admission, contributory procedures that led to diagnostic of major bleeding (CT scan, endoscopy), biological data on admission, treatments done in the emergency ward, blood transfusions, specific reversal treatment, haemostatic procedure, outcomes, length of stay in hospital, and decision about anticoagulant treatment after the haemorrhagic event. At 1 month, vital status was asked for.

2.2. Data processing and analysis

Haemorrhagic events were categorised in 3 groups: intracranial haemorrhage (ICH), gastrointestinal (GI) bleeding, and miscellaneous i.e. muscular haematoma, internal bleeding including pericardial, thoracic, peritoneal bleeding, and external bleeding including haematuria, epistaxis, scalp injury and vascular injury. The primary outcome was 1-month mortality.

Reduced dosage was defined as a dose less than 300 mg per day for dabigatran or less than 20 mg per day for rivaroxaban.

We considered a normal renal function if serum creatinine level was >90 μmol/l and/or creatinine clearance was <60 ml/min.

The study protocol was approved by the ethical committee of our hospital.

Between subgroups comparisons were performed using student's t test for parametric data, Mann–Whitney U test for non-parametric data, and the chi-square test of Fisher exact test for qualitative data. Crude relative risks were estimated along with 95% confidence interval. Statistical analysis was conducted using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). A p value of .05 was considered statistically significant.

3. Results

3.1. Population characteristics and overall outcome

During the study period (3 years), 54 patients with major bleeding while receiving a direct oral anticoagulant met our inclusion criteria.

The mean ± SD age was 81.6 ± 7.8 years (median: 84; range: 63 to 99) with a sex ratio of 1.16 (29F/25M). Hospitalization was required for 45 patients (83%) with a mean length of stay of 8.5 days. Sixteen patients needed hospitalization in intensive care units with a mean length of stay of 6.3 ± 2.9 days.

Twenty-three patients received dabigatran, 30 patients rivaroxaban, and 1 patient apixaban. Demographic and clinical characteristics according to drug are shown in Table 1.

Indication of direct oral anticoagulants was mainly atrial fibrillation. Rivaroxaban was prescribed for venous thromboembolism in 5 patients. In patients with dabigatran, reduced dosages were frequently used: 75 mg twice daily in 2 cases and 110 mg twice daily in 18 cases. In patients with rivaroxaban and with AF, dosages were reduced at 15 mg once daily in 10 cases. Apixaban was prescribed at a dosage of 5 mg twice daily. Patients treated for venous thromboembolism received rivaroxaban 20 mg once daily in 4 cases and 15 mg twice daily in 1 case.

Major types of haemorrhagic events are reported in Table 1. Other types of haemorrhage than gastrointestinal bleeding and intracranial haemorrhage were external haemorrhage (n = 8; either epistaxis (n = 3) or haematuria (n = 2) or scalp injury (n = 2) or vascular injury, or internal haemorrhage (n = 4; either haemoperitoneum (n = 3) or haemothorax), or muscular haematoma (n = 3).

Associated medications with potential drug interactions with DOAC were reported in 11 patients: antiplatelet agents in 2 cases, non-steroid anti-inflammatory drug in 1 case (with rivaroxaban), amiodarone in 6 cases — 3 with dabigatran (GI bleeding in 2 cases, ICH in 1 case) and 3 with rivaroxaban (GI bleeding in 1 case, ICH in 2 cases), and verapamil in 2 cases (GI bleeding with rivaroxaban).

At 1 month, the overall mortality was 24.1% (13 patients). Among the survivors, anticoagulant treatment was resumed in 13 patients. In 10 patients, anticoagulant therapy was definitively stopped, mostly in intracranial haemorrhage. In 17 patients, DOACs were switched for

Table 1
Demographic and clinical characteristics according to drug.

Variable	Value	All patients N = 54 number	Dabigatran N = 23 % (number)	Rivaroxaban N = 30 % (number)	Apixaban N = 1 % (number)
Gender	Female	29	52.2 (12)	53.3 (16)	100 (1)
Age (year)		54	84 ± 6	82 ± 9	83
Medical history	Hypertension	28	54.5 (12)	50 (15)	100 (1)
	Diabetes	7	14.3 (3)	18.2 (4)	0 (0)
	Stroke	14	27.3 (6)	40 (8)	0 (0)
	Haemorrhage	4	4.5 (1)	16.7 (3)	0 (0)
	Gastric ulcer	2	0 (0)	10 (2)	0 (0)
	Chronic renal insufficiency	3	10 (2)	6.7 (1)	0 (0)
Indication	Atrial fibrillation	48	95.7 (22)	83.3 (25)	100 (1)
	Others	6	4.3 (1)	16.7 (5)	0 (0)
Reduced dosage[a]		28	87 (20)	26.7 (8)	0 (0)
History of use	Unknown	11	15 (3)	30.8 (8)	0 (0)
	Less than 1 year	22	50 (10)	42.3 (11)	100 (1)
	1 to 5 years	14	35 (7)	26.9 (7)	0 (0)
Antiplatelet drug use		4	4.3 (1)	10 (3)	0 (0)
Type of haemorrhage	Gastrointestinal	27	56.5 (13)	43.3 (13)	100 (1)
	Intracranial	12	13 (3)	30 (9)	0 (0)
	Other	15	30.4 (7)	26.7 (8)	0 (0)

[a] A dose less than 300 mg per day for dabigatran, less than 20 mg per day for rivaroxaban.

vitamin K antagonists (12 cases), low molecular weight heparin (3 cases) or antiplatelet agents (2 cases).

3.2. Routine laboratory tests

On admission, all routine anticoagulant tests were abnormal with important variations. Mean activated partial thromboplastin time (aPTT), prothrombin time (PT), and INR according to each DOAC are reported in Table 2 (mean ± standard deviation, range).

In 5 patients, specific anti-factor Xa and anti-IIa assays were achieved. Clinical, haemostatic tests, therapeutic management and outcomes of these patients are shown in Table 3. Patient 3 received three successive doses of 25 U/kg of 4-factor PCCs because of persistent haemodynamic instability and bleeding, difficulty for embolization, and persistent high DOAC concentrations.

Renal function known in 49 patients was normal in 29 patients. Renal impairment was observed in 20 (40.8%) patients, 8 patients with dabigatran, 11 with rivaroxaban and 1 with apixaban. In these 20 patients, mean ± SD serum creatinine level (μmol/l) was 158 ± 63.8 and mean ± SD creatinine clearance (ml/min) was 36 ± 12.7, with no statistical difference according to the DOAC.

3.3. Intracranial haemorrhage

Twelve patients, 3 with dabigatran and 9 with rivaroxaban, had intracranial haemorrhage, spontaneous in 8 cases and posttraumatic (falls) in 4 cases. Locations of intracranial haemorrhages were subdural haematomas in 6 patients, intra-ventricular haemorrhages in 4 and lobar intracranial haematoma in 2.

Among the 10 patients without limitations of life support, reversal therapy was prescribed only in 6 cases (all with rivaroxaban, one with reduced dose). Five patients received 4-factor prothrombin complex concentrates (PCC) and 1 patient received FEIBA. Seven patients were alive at 1 month (mortality = 30/41.7% including the 2 patients with limitation of life support). Mortality at 1 month was 33% in patients with reversal therapy (2/6) and 25% without (1/4).

3.4. Gastrointestinal bleeding

Gastrointestinal bleeding was the most frequent location of major haemorrhage (n = 27; 50%).

At admission, five patients had haemodynamic failure. In those 22 patients without haemodynamic failure, mean ± SD (range) serum creatinine level (μmol/l) was 111 ± 52 (45 to 217), mean ± SD blood pressure (mm Hg) was 83 ± 17 and mean ± SD haemoglobin level (g/dl) was 7.8 ± 2.0. Creatinine clearance was > 60 ml/min in 13 patients, between 15 and 60 ml/min in 13 patients and <15 ml/min in 1.

Thirteen patients used dabigatran (11 out of 13 (85%) with reduced dose) and 13 rivaroxaban (3 (23%) with reduced dose).

Most patients (25/27) had red blood cell transfusions, mean 3.7 units (range 1 to 15). Reversal therapy was used in 2 cases: 1 patient with dabigatran received CPP and tranexamic acid, 1 patient with rivaroxaban received CPP and vitamin K.

Table 2
Routine coagulation tests on admission (mean ± standard deviation [range]).

Drug	aPTT (s)	INR	PT (s)
Dabigatran (n = 21)	61.7 ± 30 [33–177]	2.04 ± 1.8 [1.1–9.8]	22 ± 13 [13.7–76]
Rivaroxaban (n = 28)	39.5 ± 8.3 [27–60]	2.0 ± 1.0 [1.1–6.6]	21.6 ± 9 [13.9–57.5]
Apixaban (n = 1)	33	1.24	15.5

aPTT: activated partial thromboplastin time; PT : prothrombine time; INR: international normalized ratio.

Endoscopy was achieved in 24/27 patients; one patient refused investigations and 2 patients had limitation of care. In 3 patients, gastroduodenal endoscopy, colonoscopy and colonic CT scan were negative.

Causative lesions were found in 21 patients. Bleeding was located in the upper gastrointestinal tract in 9 patients, in the lower tract in 12 patients (Table 4). In patients with gastroduodenal haemorrhage, four patients had a past history of haemorrhage and one a past history of gastric ulcer; four out of those five patients experienced gastro-duodenal haemorrhage.

In 4 patients, urgent haemostatic procedure was done: haemostatic gastrectomy, mucosal resection, sclerotherapy with epinephrine injection, electrocautery therapy, each in 1 patient.

One-month mortality was low (3/27; 11%). All deaths occurred in patients with gastro-duodenal bleeding (3 out of 9 = 33%).

4. Discussion

Our study prospectively identified 54 patients with major haemorrhagic complications associated with DOAC few months after their approval by French Medicines Agencies. The increasing use of these new drugs for the treatment and prevention of thromboembolic diseases have rapidly led to the observation of haemorrhagic events.

Our study contributes to the post-marketing surveillance and adverse-event reporting system which took place in France and in others countries since the approval of DOAC [5]. Real-world data in clinical practise are needed to assess the real haemorrhagic risk of these new drugs.

All DOACs have shared similar haemorrhagic risk profiles in phase III clinical trials as compared with warfarin for the indication of stroke prevention in AF [1]. Like others, the two most important types of haemorrhagic complications reported in our study were intracranial and gastrointestinal bleedings. With the same methodology and inclusion criteria, if we compare the repartition of major bleeding with VKA in our initial historical cohort [4], it appears that intracranial bleeding incidence is lower than gastrointestinal bleeding with DOAC: 32.6% and 31.2% respectively for gastrointestinal and intracranial bleedings with VKA versus 50% et 22.2% with DOAC in the present study.

These findings are consistent with recent meta-analysis on the risk of major and life-threatened haemorrhagic complications with DOAC compared with warfarin: all studies have shown a lower risk of intracranial haemorrhage with a reduction by one-half and an identical or slightly higher risk of gastrointestinal bleeding [1,2,6]. These results were confirmed with dabigatran in the real world in the Danish register [7,8], and, recently, in a large cohort of elderly patients enrolled in Medicare [9].

In our study, the most common site of bleeding was gastrointestinal. In these patients, details of our medical records have shown usual causative lesions. Among other haemorrhagic complications, we reported a rare case with spontaneous splenic haemorrhage with rivaroxaban. One identical case with dabigatran has been reported by Moore et al. [10].

Median age of our population was 84 years, which constitutes an important risk factors for bleeding complications with DOAC and confirms the strong link between increasing age and risk of major bleeding [5,11]. Renal function was altered in 41% of our patients. Renal impairment is also a well-known increasing risk factor of bleeding for each DOAC [12].

Clinical characteristics, blood volume replacement and outcomes were similar to patients with major haemorrhage associated with VKA described in our previous report [4]. Mean stay of length (8.5 days) was identical in our studies, in contrast with Berger's results showing a lower stay of length with DOAC compared with warfarin [13].

Thirteen patients died (24.1%). As previously reported, mortality was higher in the group of patients with intracranial haemorrhage [14,15,16]. These results would be of clinical importance. The 1-month

Table 3
Clinical and biological characteristics and therapeutic management of patients with DOAC assays.

Case, gender, age	DOAC	Bleeding complications	Haemostatic tests on admission	DOAC levels ng/ml	Reversal therapy	RBC transfusion (N. units)	Creatinine clearance (ml/min)	Outcome at 1 month
Case no. 1 F78	Dabigatran 150 mg × 2	Haemorrhagic shock, GI bleeding	aPTT = 177 s INR = 9.8 PT = 75.5 s	>500 on admission >500 H + 24	PCC 50 U/kg	5	18	Alive
Case no. 2 F77	Dabigatran 110 mg × 2	Epistaxis	aPTT = 59 s INR = 2.1 PT = 23.2 s	220.5 on admission 92.8 H + 18	–	3	>60	Alive
Case no. 3 F85	Rivaroxaban 15 mg × 1	Haemorrhagic shock, Splenic haematoma with haemoperitoneum	aPTT = 40 s INR = 2.3 PT = 24.8 s	153.5 on admission 85.54 H + 7 67.7 H + 11 56.9 H + 15 36.4 H + 19	PCC 25 U/kg PCC 25 U/kg PCC 25 U/kg	4	>60	Alive
Case no. 4 F87	Rivaroxaban 10 mg × 1	Haemorrhagic shock, aortic aneurysm	aPTT = 49 s INR = 3.7 PT = 35.8 s	471.9 on admission	PCC 25 U/kg	1	?	Dead (limitation of life support)
Case no. 5 F83	Apixaban 5 mg × 2	GI bleeding	aPTT = 33 s INR = 1.24 PT = 15.5 s	270.3 on admission	–	3	47.6	Alive

DOAC: direct oral anticoagulant; PT: prothrombin time; INR: international normalized ration; aPTT: activated partial thromboplastin time; PCC: prothrombin complex concentrates; RBC: red blood cells; GI: gastrointestinal.

mortality was 20.3% in the subgroup of patients with major haemorrhages associated with VKA in our initial 2011–2012 cohort [4].

As we have shown, routine laboratory coagulation tests were abnormal in all patients. Every DOAC induced interferences with routine monitoring like aPPT and PT. These anomalies are unreliable for estimation of overdose of DOAC. No real correlation exists between the reversal of laboratory parameters and the reversal of bleeding. Standard coagulation assays appear not to be predictive of the ability of reversal agents to decrease bleeding related to DOAC [17]. So, we do not take them into account for the treatment of the haemorrhagic event in current practise.

The therapeutic management of haemorrhagic event with DOAC is based on nonscientific considerations. Current recommended pathways for the management of DOAC bleeding include discontinuation of treatment, local or surgical haemostatic control, blood transfusion, endoscopic or surgical intervention, local compression, and haemodynamic support [6,12,16–19]. We favoured this logical approach in the majority of our patients.

In life-threatening bleeding, haemostatic agents such as activated prothrombin complex concentrate (aPCC or FEIBA) or nonactivated prothrombin complex concentrates (PCC) have been proposed [20]. However, these reversal strategies for DOAC have not been validated because of sparse clinical experience [21].

In France, proposals based on drug plasma concentrations of dabigatran or rivaroxaban and aPCC or PCC with high dosages (50 UI/kg) were made by the Working Group on Perioperative Haemostasis. If the drug dosage is not available, worse propositions are based on the usual tests (aPTT and PT) [22]. In 5 patients with major bleeding, DOAC concentrations were available. All concentrations were high, markedly above the threshold of 30 ng/ml which corresponds to the safe limit of the chromogenic anti-Xa assay. These dosages can help decision-making of emergency clinicians for the management of life-threatened bleeding, as we showed in some patients (Table 3).

In our study, reversal therapy was used in serious bleeding in a critical organ, especially in patients with intracranial bleeding. The small number of patients did not allow to show any statistical benefit on mortality. However, the dosage of PCC we have prescribed was lower than recommended [22].

Specific antidotes for dabigatran and factor Xa inhibitors are under development; they may contribute to decrease the mortality of bleeding complications associated with DOAC.

Neither haemodialysis, nor oral activated charcoal, were performed in patients with dabigatran. One patient with rivaroxaban received anti-fibrinolytic agent (tranexamic acid) as proposed by Siegal et al. [17].

Table 4
Gastrointestinal (GI) haemorrhage associated with DOAC: causative lesions (n = 21).

	Dabigatran	Rivaroxaban	Apixaban	Total
Upper GI lesion				
Gastroduodenal ulcer	2	4		6
Duodenal diverticulum		1		1
Gastric erosive lesion	1	1		2
Lower GI lesion				
Colon cancer	2		1	3
Colonic diverticulum	2	2		4
Colonic polyp	1	1		2
Villous rectal adenoma		1		1
Colonic haemangioma	1			1
Colonic ulcer	1			1

5. Conclusion

Our prospective study have shown the rapid occurrence of major haemorrhagic event associated with DOAC admitted in emergency department few months after their approval, particularly in 2013. Major bleeding occurred in a very old population with frequent renal impairment. One-fourth of patients died 1 month after haemorrhagic event. Intracranial haemorrhage and gastrointestinal bleeding were the two main locations. Emergency management of bleeding was based on general measures and blood transfusions. Coagulation factor replacement with aPCC or PCC was used in life threatening bleeding as recommended.

Our study contributes to a better knowledge of the major adverse effects of these new drugs and implemented the reports in the pharmacovigilance centres. Further pharmaco-epidemiologic studies are still required.

Authors' contributions

Jacques BOUGET contributed to the concept and the design of the study, the acquisition of data, and to the writing of the manuscript. Emmanuel OGER contributed to analysis and interpretation of data

and participated in review and revision. The final version of the manuscript was approved by the authors.

Conflicts of interest

No conflict of interest was reported from the authors regarding the content of this manuscript.

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