Thrombosis Research 136 (2015) 1190–1194

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

# Emergency admissions for major haemorrhage associated with direct oral anticoagulants

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ARTICLE INFO

*Article history:*
Received 22 June 2015
Received in revised form 14 September 2015
Accepted 28 October 2015
Available online 29 October 2015

*Keywords:*
Direct oral anticoagulant
Haemorrhage
Gastrointestinal bleeding

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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http://dx.doi.org/10.1016/j.thromres.2015.10.036
0049-3848/

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.