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Emergency admissions for major haemorrhage associated with antithrombotics: A cohort study ☆

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ABSTRACT

Introduction: to describe antithrombotic-related major haemorrhage, therapeutic management and outcomes in patients admitted to an emergency department of a teaching hospital.
Material and method: This prospective cohort included patients older than 16 years with antithrombotic-related major haemorrhage identified by monthly diagnostic codes computerised requests. Major haemorrhage was defined by at least one the following criteria: unstable hemodynamic, haemorrhagic shock, uncontrollable bleeding, need for transfusion or haemostatic procedure, or a life threatening location.
Results: between January 1, 2011 and December 31, 2012, 913 patients met the inclusion criteria (1.2 patients per day), median age 82. Oral anticoagulants alone or in combination were used by 429 patients, antiplatelet agents (alone or dual therapy) by 420 patients, and parenteral anticoagulants by 64 patients. Major haemorrhages were: gastrointestinal bleeding (37.5%), intracranial haemorrhage (34.4%), muscular hematoma (9.4%), external haemorrhage (16.9%) and internal haemorrhage (1.9%). At 1 month, 179 patients (19.8%) died, mostly patients with intracranial haemorrhage (64.2%). Prognostic factors for death were age and Glasgow coma scale at admission for intracranial haemorrhage, age and mean arterial pressure at admission for other major haemorrhages. Oral anticoagulant therapy was a predictor for death in intracranial haemorrhages. Reversal therapy was initiated in only 50.5% of patients with vitamin K antagonists, without effect on the mortality rate.
Conclusion: This study shows the magnitude and the severity of antithrombotic-related major haemorrhage. The high mortality rate supports careful awareness in individual risk benefit assessment, especially for elderly.

Introduction

Antithrombotics, i.e. oral and parenteral anticoagulants as well as antiplatelet agents, have demonstrated significant benefits in preventing venous or arterial thrombotic events, especially in coronary disease, stroke, atrial fibrillation, venous thromboembolism and mechanical heart valves [1]. These drugs are commonly prescribed and their long term use is increasing, particularly in elderly.

Bleeding represent the most well-known and feared complications of antithrombotics. Numerous studies on adverse drug events reported anticoagulants as the first medication class implicated in haemorrhage and specifically intracranial haemorrhage (ICH) which often results in substantial morbidity and mortality [2]. Using adverse drug events from a National Surveillance System, Budnitz et al demonstrated that warfarin and oral antiplatelet agents are respectively the first and the third medications leading to emergency department and hospitalization in adults 65 years of age or older [3]. For antiplatelet agents, gastrointestinal bleeding and intracranial haemorrhage are well known [4–6].

Emergency departments are unique to describe antithrombotic-related major haemorrhage. We report the results of a prospective cohort that aimed to describe antithrombotic-related major haemorrhage, diagnostic process, clinical and therapeutic management as well as 1-month outcome.

Material and Methods

Patient Selection and Definitions

Patients older than 16 years admitted in the emergency department of our teaching hospital with antithrombotic-related major haemorrhage were consecutively included between January 1, 2011 and December 31, 2012. Patients were identified through haemorrhagic symptoms at emergency admission. Computerised requests based on several related-haemorrhagic diagnostic codes and specific emergency

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therapies were made every month on electronic health records. Then, criteria of major bleeding were required and antithrombotic treatment searched.

According to the French National Authority for Health (Haute Autorité de Santé - HAS) [7], major bleeding was defined by at least one of the following criteria : hemodynamic instability (systolic arterial pressure <90 mmHg 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-threatened bleeding such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, thoracic bleeding, compressive muscular hematoma, acute gastrointestinal bleeding. In addition to these criteria, we considered major bleeding in case of epistaxis if at least two procedures of nasal packing were needed and in case of hematuria if the bleeding continued during more than 12 hours despite bladder washing.

All antithrombotic drugs, alone and in combination were eligible whatever their indication and their dosage.

Patients with major bleeding events associated with antithrombotic during hospitalization, patients with intentional overdose with antithrombotic drugs 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, time between admission and diagnosis, time between admission and reversal therapy, outcomes, length of stay in hospital, and decision about antithrombotic treatment after the haemorrhagic event. At 1 month, clinical data about hemorrhagic or ischemic event and vital status were asked.

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

Data Processing and Analysis

Three subgroups were defined depending on antithrombotic medications: group1: Oral anticoagulant (OA) group including patients with oral vitamin K antagonist and new oral anticoagulant, alone and in combination with other antithrombotic drugs; group 2: Antiplatelet (AP) group including patients with antiplatelet therapy only, either alone or dual therapy; group 3: Parenteral anticoagulant (PA) group including patients with unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, danaparoid, alone and in combination with antiplatelet therapy.

Haemorrhagic events were firstly divided in 5 groups: intracranial haemorrhage, gastrointestinal bleeding, muscular hematoma, internal bleeding including pericardial, thoracic, peritoneal bleeding, and external bleeding including hematuria, epistaxis, scalp injury, vascular injury. Then, two subgroups were defined: patients with intracranial haemorrhage and patients with other major bleeding

The primary outcome was 1-month mortality.

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 for qualitative data. Crude relative risks were estimated along with 95% confidence interval. Prognostic factors for death at 1-month were defined in the overall population and in the subgroups of patients with intracranial haemorrhage and patients with other bleeding than intracranial haemorrhage. Multivariate logistic models were run in subgroups of patients with intracranial haemorrhage and of patients with other major bleeding to assess the predictors of death. 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.

Results

Population Characteristics

In 2011 and 2012, 98,377 adult patients were admitted in our emergency department. Nine hundred and thirteen patients (0.9%) with major bleeding while receiving at least one antithrombotic drug were analysed, which represented 1.2 patients per day. During the study period, there were no monthly variations. The mean age was 80 ± 10 years (range : 21-103); median, 82 years) with a sex ratio of 1.1. Hospitalization was required for 728 patients (79%) with a mean length of stay of 8.5 ± 14.2 days, including 1.3 ± 3.9 days in intensive care units.

Demographic characteristics and indications of antithrombotics, according to the therapeutic subgroups, are reported in Table 1. Among 913 patients, 152 (17.2%) had a combination of antithrombotic agents. The duration of prescription was unknown in 46.3% of cases. Gastrointestinal bleeding and intracranial haemorrhage (ICH) represented more than 70% of major haemorrhagic events (Table 2). There was a statistically significant association between types of antithrombotics and types of haemorrhage ($p < .0001$): AP-related haemorrhages were mostly ICH (n = 164, 39%) and gastrointestinal bleeding (n = 179, 42%) whereas OA-related haemorrhages were mostly external haemorrhages or muscular hematomas (n = 147, 34%), gastrointestinal bleeding (n = 140, 33%) and ICH (n = 134, 31%). The mechanism of the ICH, known in 307 patients, was traumatic in 44.6% of cases, mostly a fall from standing height, spontaneous in 45.6%, impossible to determine in 9.4%. In traumatic ICH, there were more patients with AP than OA (60% versus 40%). Frequencies of AP and OA were similar in those patients with spontaneous ICH (51.5% versus 48.5%).

Table 1
Demographics and clinical characteristics.

Patients	n	%
Gender		
Male	480	52.6
Female	433	47.4
Age, years		
21 – 60	44	4.8
61 – 70	83	9
71 – 80	260	28.5
81 – 103	526	57.6
Indication of antithrombotics		
Atrial fibrillation	371	51.6
Stroke	164	15.6
Myocardial infarction	162	24.7
Venous thromboembolism	115	15.7
Peripheral arterial disease	75	11.3
Mechanical heart valve	46	8.5
Others	121	16.3
Duration of antithrombotic medication		
<1 year	117	12.8
1> years >5	158	17.3
>5 years	215	23.6
Unknown	423	46.3
Type of antithrombotic agents		
Oral anticoagulant	429	47.0
Vitamin K antagonist	427	46.8
alone	*353*	0.2
in combination with antiplatelet	*61*	
other combination	*12*	
New oral anticoagulant	2	
Antiplatelet agents	420	46.0
alone	*380*	
dual therapy	*39*	
Parenteral anticoagulant	64	7.0
Unfractionned heparin	*5*	
Low molecular weight heparin	*43*	
Fondaparinux	*15*	
Danaparoid	*1*	