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To cite this version:

Jacques Bouget, Emmanuel Oger, Nathalie Nicolas. Emergency admissions for major haemorrhage associated with antithrombotics: A cohort study. Thrombosis Research, 2015, 135 (1), pp.84-89. 10.1016/j.thromres.2014.10.029 . hal-01085271

HAL Id: hal-01085271

https://univ-rennes.hal.science/hal-01085271

Submitted on 21 Nov 2014

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Emergency admissions for major haemorrhage associated with antithrombotics: a cohort study.

Jacques BOUGET [a], MD, Emmanuel OGER [b,c], MD, PhD, Nathalie NICOLAS [a], MD

Authors affiliation: [a] University of Rennes-1, Rennes University Hospital, Emergency Department; [b] University of Rennes-1, Rennes University hospital, Department of Clinical Pharmacology; [c] INSERM, CIC-1414, Pharmacoepidemiology team (CTAD-PEPI), Rennes, France.

Corresponding author: Jacques BOUGET, MD, Emergency department, Pontchaillou Hospital, 35033 Rennes, France (Jacques.bouget@chu-rennes.fr) tel. +33299284321 fax. +33299282432

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. Nathalie NICOLAS contributed to the acquisition of data. Emmanuel OGER contributed to analysis and interpretation of data and participated in review and revision. All authors approved the final version of the manuscript.

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

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Abstracts

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.

Word count: 237/250

Key words (6): antithrombotic, major bleeding, anticoagulant, antiplatelet, emergency department, intracranial haemorrhage.

Emergency admissions for major haemorrhage associated with antithrombotics: a cohort study.

Word count 5,375 /6,000

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 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%).

Predictors of 1-month mortality

At 1 month, data from 903 documented medical records were analysed. In this population, 179 patients died at 1 month (19.8 %). Fifty-five patients died in the emergency ward. Death occurred within the first 3 days of hospitalization in 81 patients. The distribution of death according to the type of haemorrhagic events showed that intracranial haemorrhage was responsible of the most number of death (115/179 patients, 64.2%). Among 267 patients with a known ICH mechanism and a known vital status at 1 month, 1-month mortality was higher in spontaneous ICH than in traumatic ICH: 45.9% (62/135) vs. 26.5% (35/132), $p = 0.001$. Among 314 patients with ICH, 27 (8.6%) had limitation of life support; 22 patients (7.7%) out of the 287 remaining patients underwent surgery: 18 out of those 22 patients were alive at one month (81.8%) compared to 178 out of 265 patients who did not have surgery (67.2%), $p = 0.15$. Among 342 patients with GI bleeding, 61 had an invasive therapy (endoscopy, n = 42; surgery, n = 20; embolisation, n = 3; of note 4 patients had two procedures); 59 out of those 61 patients were alive at one month (96.7%) compared to 249 out of 281 patients who did not have invasive therapy (88.6%), $p = 0.055$.One-month mortality was not associated with the type of antithrombotic agents (table 3).
In univariate analysis, prognostic factors for 1-month mortality in case of intracranial haemorrhage were age, Glasgow coma scale (GCS) score, the type of antithrombotic agents (OA), time between admission and diagnosis and time between admission and biological results (table 4). OA was associated with a 1.4-fold increased risk for 1-month mortality compared to AP: RR = 1.5 (95%CI, 1.1 to 2.0); relative risk for PA compared to AP was 1.2 (95%CI, 0.6 to 2.5). Prognostic factors for 1-month mortality after other haemorrhagic events were age, mean arterial pressure at admission and type of antithrombotic agents (table 4). PA

was associated with a 1.7-fold increased risk for 1-month mortality compared to AP: RR = 1.7 (95%CI, 0.8 to 3.3); relative risk for OA compared to AP was 0.8 (95%CI, 0.5 to 1.4). Adjusting for age and GCS through multivariate logistic regression, OA remained statistically associated with ICH 1-month mortality compared to AP (p = 0.0451) and PA did not reached statistical significance for other haemorrhagic event 1-month mortality compared to AP (p = 0.57).
Among surviving patients at 1 month (724), antithrombotic treatment was continued without modifications in 382 patients (52.8%), with modifications in 125 patients (17.3%), discontinued in 171 patients (23.6%), not determined in 46 patients (6.3%). Antithrombotic treatment was stopped in all patients with ICH.

Oral anticoagulant group: characteristics, clinical and therapeutic management

Demographic and clinical characteristics of the 3 treatment groups are reported in table 5. Most of oral anticoagulants were vitamin K antagonists (427/429). Vitamin K antagonists were fluindione in 68% of cases, warfarine in 38% of cases and acenocoumarol in 3% of cases. In 63 patients, OA was in combination with AP. Only two patients were taking new oral anticoagulant (dabigatran etexilate) for prevention of stroke in atrial fibrillation and they were included at the end of 2012: a 82 years old man with major fatal hematuria, and a 80 years old man with gastrointestinal bleeding, alive at 1 month.

At admission, the international normalized ration (INR) was in the therapeutic range (between 2 and 3) in 41.9% of cases, under the range in 18.6% and above in 39.5%. Median [p25-p75] INR value was slightly higher among patients with ICH who died within one month compared to those who were alive: 2.6 [2.1-3.2] vs. 2.4 [1.9-2.9] (p = 0.066). The same pattern was observed in other type of haemorrhage: 3.7 [2.4-7.4] vs. 2.8 [2.2-4.2] (p = 0.031).
Reversal therapy was initiated in only 215 patients (50.5%); the complete recommended treatment, that is prothrombin complex concentrate (PCC) at a dose equal or superior to 20 IU/kg in association with 5 or 10 mg of vitamin K, was prescribed only in 80 patients (19.1%). This reversal treatment was not significantly associated with 1-month mortality considering only patients with no limitation of life support: 5/21 (23.8%) vs. 11/40 (27.5%) in patients with ICH and 6/70 (8.6%) vs. 7/68 (10.3%) for other type of haemorrhage.

Two-hundred and two patients needed blood transfusions (mean 2.3 units of red cells), for gastrointestinal bleeding in 101 patients, muscular hematomas in 39 patients, epistaxis in 17 patients. Fifty patients required surgery.
At 1 month, OA therapy was continued in 53% of cases and stopped in 24% of cases. In 23% of cases, treatment was changed, switch with antiplatelet agents or stop of combination.

Antiplatelet group: characteristics, clinical and therapeutic management

In the antiplatelet group (420 patients), aspirin represented 88% of cases, clopidogrel 20% of cases, dual therapy 9% of cases. Demographic and clinical characteristics, number of red cell transfusions, hospitalization rate and mortality rate were not different compared to patients from the oral anticoagulant group (table 5). No platelet transfusion was prescribed.
At 1 month, antiplatelet agents were continued in 61% of cases, discontinued in 24% of cases. In 15% of cases, the treatment was modified, that is stop of the dual therapy or switch with other antiplatelet drugs.

Parenteral anticoagulant group: characteristics, clinical and therapeutic management

In the parenteral anticoagulant group (64 patients), drugs were: LMWH in 43 patients, UFH in 5 patients, fondaparinux in 15 patients and danaparoid in one patient; the dose was curative in 37 patients (57.8%), mainly with LMWH (n = 23) and fondaparinux (n = 10) whereas only four patients had curative UFH dose. The main indication was the venous thromboembolic disease. Glasgow coma scale score, mean arterial pressure, mean haemoglobin level at admission were different with patients of other groups (not significant). No reversal treatment (protamin sulfate) was initiated. At 1 month, parenteral anticoagulants were continued in 22 patients, stopped in 20 patients.

Discussion

With more than one patient per day admitted in our emergency ward on a two-year period, our study highlighted the magnitude of major bleeding associated with antithrombotics, whatever the antithrombotic drug.

The patient's median age was high (82 years old), reflecting the increasing use of antithrombotic in elderly in all their indications, as previously reported [4]. Particularly, the number of patients with atrial fibrillation will progressively increase in the next years. Consequently, the number of major bleeding will still increase in this frail population, leading to an important morbidity and mortality. Despite this increased haemorrhagic risk secondary to age, the elderly still have the most important benefits of antithrombotics, even after a major bleeding event [8]. In survivors, we observed that 53 % of the oral anticoagulant group and 61% of the antiplatelet group continued the same antithrombotic treatment 1 month after the haemorrhagic event.

In our study, 152 patients were taking more than one antithrombotic drugs with various combinations. Even if the combination of antithrombotics increase the haemorrhagic risk [9, 10] the various combination would have complicated the analysis of our study population. Thus, to compare the different antithrombotic agents, we classified our patients in only three therapeutic groups, considering that the haemorrhagic risk was most important with oral and parenteral anticoagulants than with antiplatelet agents [1, 11]. We identified 64 patients with major bleeding associated with parenteral anticoagulant, especially heparins and fondaparinux. To our knowledge, this was the first report on major bleeding in an ambulatory population with these antithrombotics. Usually, most data came from multicenter clinical trial [13]. Our results showed that the corresponding population was different from patients of others therapeutic groups, i.e. more severity, increased mortality rate in patients with mainly venous thromboembolic indication. In this group, the distribution of the different haemorrhagic complications was equivalent to other group of antithrombotics, as previously reported [14].

In the therapeutic management of the hemorrhagic events, there were an important number of blood transfusions, with numerous haemostatic procedures (surgery, endoscopic procedure). Indications of blood transfusions were left to physician appreciation. In the oral anticoagulant group, reversal therapy was used in only 50.5 % of cases, despite the national guidelines [7]. In ICH associated with oral anticoagulant, reversal therapy with PCC and vitamin K was specially used because of the poor prognosis of this bleeding event. Nevertheless, the mortality rate was not different with or without reversal therapy in case of ICH. In the antiplatelet group, no platelet transfusion was needed, according to the recent systematic review in traumatic and spontaneous ICH [15].

Gastrointestinal bleeding was the first major haemorrhagic events in our study, with a similar number associated with OA and AP. Even if this bleeding risk was well known, international trial and meta-analysis have reported various risk levels according to the antithrombotic drugs. Relative risk of gastrointestinal risk was estimated at 1.8 and 1.6 for respectively aspirin and clopidogrel, two-fold higher for oral anticoagulant therapy, especially when the INR value is high [5, 16, 17]. In our OA group, INR value was not a prognostic factor. Dangerous combinations such as OA + AP or dual antiplatelet therapy induced a more 2-fold higher risk of gastrointestinal bleeding [10, 12].

In 314 patients (34.4 %), the haemorrhagic event was intracranial, spontaneous or traumatic, leading to a dramatic prognosis (64.2% of dead patients at 1 month had IHC). The number of patients with OA and AP was similar, but, the multivariate OR for death in ICH patients was significantly unfavourable at one month in OA versus AP (OR = 1.89 (95%CI 1.01-3.54). This high mortality has been reported elsewhere [18, 19] and seemed to be dependant to the mechanism of the ICH and to the antithrombotic medication. In a multicenter Italian study in emergency departments, Baldi and al reported a mortality rate of 44% in post traumatic IHC (41% with AP and 51% with OA), and 58% in spontaneous ICH (51% with AP and 69% with OA [4]. Like others, we found that age and Glasgow coma scale will be strong prognostic factors in patients with intracranial haemorrhage. In case of ICH, time between admission and diagnosis and time between admission and first biological results were significantly shorter in patients who died, which could be explained by a more severe condition on admission.
In head trauma, oral anticoagulant led to 10-fold higher incidence of intracranial haemorrhagic lesions (3 versus 29%), reaching a mortality rate near to 60% [20]. Old age increased furthermore this rate (OR = 1.2 for each increase of 10 years) [21]. As reported by Dowlatshahi et al [22] and as shown in our results, the mortality did not seem to be affected by complete reversal therapy.

For antiplatelet drugs, there is a great heterogeneity for establishing a strong link between ICH and this medication, because of various inclusion criteria, different methodology, severity at inclusion, mechanism, outcomes. Nevertheless, antiplatelet drugs appeared to be a risk factor for IHC in patients with minor head trauma. In a recent meta-analysis, Bachelor et al [23] reported an important overall relative risk of aspirin in all head trauma (OR = 2.43), higher than clopidogrel (OR = 1.55); other studies have reported opposite results, with a more important risk with clopidogrel than with aspirin [24, 25]. Whatever these various risk assessments, the old age and the Glasgow coma score appeared to be strong prognosis factors, as shown in our results [26]. In spontaneous ICH, the systematic review of Thompson et al reported an increase of mortality rate induced by antiplatelet agents (40% in univariate analysis, 27% in multivariate analysis) and a higher poor prognosis (respectively 29 and 10%) [27].

Strengths

The selection method used in our study would have contributed to increase the number of haemorrhagic events. We selected patients firstly from the haemorrhagic symptom at emergency admission, in contrast with most studies on this subject which screened patients from the medication. Our method was quite similar with the study reported by Budnitz et al, in which coders reviewed clinical records of each emergency department visit to identify adverse drug events [3]. Heterogeneity of codes compelled to use a list of about forty different diagnostic codes relative to haemorrhagic events and pathologies. This first step was then completed by the search for the criteria of major bleeding and finally by the identification of the antithrombotic medication, information often missed in the emergency medical record. This method could explain the equal number of major bleeding with oral anticoagulant and antiplatetet drugs, with a quite equivalent distribution of types of haemorrhage, particularly intracranial haemorrhage and gastrointestinal bleeding. In the same way, it could explain the relative important group of patients with parenteral anticoagulants.

Limitations

Our study was monocentric and in part retrospective. Computer requests were made every month in a retrospective manner, which could explain a lost of some data concerning medical history and antithrombotic duration. However, this design could provide an unbiased observation of real life behaviour because patients' management was not influenced by the knowledge of an ongoing study. Because of the heterogeneity of diagnostic codes, we listed about 40 different symptoms and diseases related to haemorrhagic events.
We used criteria of major bleeding recommended by the French National Authority for Health (Haute Autorité de Santé - HAS) [7] rather than criteria of the International Society on Thrombosis and Haemostasis (ISTH) defined by Schulman et al [28]. We thought that all these criteria were close to each other, which would not have modified our population. In addition, we thought that the fall in haemoglobin level of 20g/L or more is a less suitable criterion for an emergency recruitment.

Conclusion

Our study shows the magnitude of major bleeding in a very old population taking antithrombotics, admitted in the emergency department of a teaching hospital. Oral anticoagulants and antiplatelet drugs are equally implicated in this iatrogenic pathology. The severity is attested by a high mortality (about 20%) at one month after the haemorrhagic event. Intracranial haemorrhage, age and Glasgow coma scale at admission are prognostic factors. In case of intracranial haemorrhage, oral anticoagulant is a predictor of death.
The high frequency of these events and the important mortality rate suggest a great vigilance in risk benefit imbalance of antithrombotic medication for individual patients, especially for elderly.

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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*	
in combination with antiplatelet	*61*	
other combination	*12*	
New oral anticoagulant	2	0.2
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*	

Table 2 Distribution of haemorrhagic events

Type of haemorrhage	**N**	**%**
Gastrointestinal bleeding	**342**	**37.5**
Intracranial haemorrhage	**314**	**34.4**
Muscular hematoma	**86**	**9.4**
External haemorrhage	**154**	**16.9**
Epistaxis	*47*	*5.1*
Hematuria	*36*	*3.9*
Scalp injury	*19*	*2.1*
Vascular injury	*11*	*1.2*
Other	*41*	*4.5*
Internal haemorrhage	**17**	**1.9**
Thoracic	*7*	*0.8*
Peritoneal	*6*	*0.6*
Pericardial	*4*	*0.4*

Table 3 Hemorrhagic events and antithrombotic drugs according to 1-month mortality

	Dead patients N = 179	Alive patients N = 724	
Haemorrhagic event	n (%)	n (%)	**< 0.0001**
Intracranial haemorrhage	115 (64.2)	199 (27.5)	
Gastrointestinal bleeding	34 (19.0)	308 (42.5)	
Muscular hematoma	8 (4.47)	73 (10.1)	
External haemorrhage	20 (11.2)	130 (18.0)	
Internal haemorrhage	2 (1.12)	14 (1.93)	
Treatment group			0.5592
OA	87 (48.6)	335 (46.3)	
AP	77 (43.0)	340 (46.9)	
PA	15 (8.38)	49 (6.79)	

OA : oral anticoagulant ; AP : antiplatelet ; PA : parenteral anticoagulant;

1
2
3
4

Table 4 Prognostic factors of 1-month mortality in univariate analysis; A: in patients with intracranial haemorrhage (n=314). B: in patients with other haemorrhagic events (n=579)

A

Characteristic	Died patients N = 115	Alive patients N = 199	
Treatment			0.0293
OA	60 (52.2)	74 (37.2)	
AP	49 (42.6)	115 (57.8)	
PA	6 (5.22)	10 (5.03)	
Clinical characteristics			
Female	60 (52.2)	101 (50.7)	0.8083
Age, years	81.6 ± 8.8	79.4 ± 10.0	**0.0545**
Glasgow coma scale	8 [3-15]	15 [3-15]	**< 0.0001**
Hemoglobin level, g/dL	13.1 ± 1.8	13.0 ± 1.7	0.8772
Mean arterial pressure (mmHg)	107 ± 25	97 ± 18	**0.0004**
Time admission/diagnosis (hours)	5.9 ± 9.8	9.4 ± 13.2	**< 0.0001**
Time admission/biological data (hours)	1.3 ± 1.7	2.7 ± 5.5	**< 0.0001**
Reversal therapy (VKA, n = 75)	17 (58.6)	29 (63.0)	0.7017

B

Characteristic	Died patients N = 64	Alive patients N = 525	
Treatment			0.1561
OA	27 (42.2)	261 (49.7)	
AP	28 (43.7)	225 (42.8)	
PA	9 (14.1)	39 (7.46)	
Clinical characteristics			
Female	29 (45.3)	236 (44.9)	0.9564
Age, years	83.2 ± 9.2	79.7 ± 10.5	**0.0024**
Hemoglobin level, g/dL	8.7 ± 2.2	8.8 ± 2.3	0.7662
Mean arterial pressure (mm Hg)	70 ± 19	78 ± 16	**0.0034**
Time admission/diagnosis (hours)	9.9 ± 14.8	7.9 ± 12.1	0.9162
Time admission/biological data (hours)	1.7 ± 1.3	1.9 ± 1.4	0.2147
Reversal therapy (VKA, n = 138)	6 (46.1)	64 (51.2)	0.7291

OA : oral anticoagulant ; AP : antiplatelet ; PA : parenteral anticoagulant; VKA: vitamin K antagonist

Table 5 Characteristics of patients according to therapeutic groups.

Characteristics n (%)	OA N = 429	AP N = 420	PA N = 64	p-value
Type of haemorrhage				<.0001
Gastrointestinal bleeding	140 (32.6)	176 (41.9)	26 (40.6)	
Intracranial haemorrhage	134 (31.2)	164 (39.0)	16 (25.0)	
External haemorrhage	88 (20.7)	54 (12.8)	12 (18.7)	
Muscular hematoma	57 (13.3)	17 (4.0)	12 (18.7)	
Internal haemorrhage	7 (1.6)	9 (2.1)	1 (1.6)	
Indication				
Atrial fibrillation	304 (70.9)	55 (13.1)	12 (18.7)	
Stroke	48 (11.2)	106 (25.2)	12 (18.7)	
Myocardial infarction	45 (10.5)	108 (25.7)	11 (17.2)	
Venous thromboembolism	71 (16.5)	21 (5)	21 (32.8)	
Peripheral arterial disease	20 (4.6)	49 (11.7)	10 (15.6)	
Mechanical heart valve	36 (8.4)	10 (2.4)	0	
Others	8 (1.9)	97 (23.1)	20 (31.2)	
Duration of antithrombotic				<.0001
< 1year	48 (11.2)	36 (8.6)	33(51.6)	
1> years >5	76 (17.7)	73 (17.4)	9 (14.1)	
> 5 years	100 (23.3)	108 (25.7)	5 (7.8)	
Unknown	202 (47.1)	202 (48.1)	18 (28.1)	
Clinical characteristic				
Female, n (%)	207 (48.2)	194 (46.2)	30 (46.9)	0.796
Age, years	79.7 ± 10.3	80.8 ± 9.5	78.8 ± 12.8	0.279
GCS - median [min-max]	15 [3-15]	15 [3-15]	14 [3 – 15]	0.347
Mean arterial pressure (mmHg)	85 ± 22	87 ± 21	77 ± 20	0.001
Haemoglobin level, g/dL	10.2 ± 2.9	10.3 ± 3.0	9.2 ± 2.3	0.028
Reversal therapy	215 (50.1)	-	-	
Blood transfusion Number of units (mean)	202 (47.1) 2.3	197 (46.9) 2.0	36 (56.2) 1,5	
Hospitalization	337 (78.5)	337 (80.2)	58 (90.1)	
Mean length of stay (day)	8.5 ± 11.4	8.8 ± 17.9	9.1 ± 11.2	0.733
Outcomes at 1 month				0.345
Lost of follow-up	7 (1.6)	3 (0.7)	0 (0)	
dead	87 (20.3)	77 (18.3)	15 (23.4)	
alive	335 (78.0)	340 (80.9)	49 (76.5)	

OA= oral anticoagulant; AP= antiplatelet; PA= parenteral anticoagulant. GCS: Glasgow coma scale, in patients with intracranial haemorrhage