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

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20 Jacques BOUGET contributed to the concept and the design of the study, the acquisition of  
21 data, and to the writing of the manuscript. Nathalie NICOLAS contributed to the acquisition  
22 of data. Emmanuel OGER contributed to analysis and interpretation of data and participated  
23 in review and revision. All authors approved the final version of the manuscript.

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

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6 **Abstracts**

7  
8 **Introduction:** to describe antithrombotic-related major haemorrhage, therapeutic  
9 management and outcomes in patients admitted to an emergency department of a teaching  
10 hospital.

11 **Material and method:** This prospective cohort included patients older than 16 years with  
12 antithrombotic-related major haemorrhage identified by monthly diagnostic codes  
13 computerised requests. Major haemorrhage was defined by at least one the following criteria:  
14 unstable hemodynamic, haemorrhagic shock, uncontrollable bleeding, need for transfusion or  
15 haemostatic procedure, or a life threatening location.

16 **Results:** between January 1, 2011 and December 31, 2012, 913 patients met the inclusion  
17 criteria (1.2 patients per day), median age 82. Oral anticoagulants alone or in combination  
18 were used by 429 patients, antiplatelet agents (alone or dual therapy) by 420 patients, and  
19 parenteral anticoagulants by 64 patients. Major haemorrhages were: gastrointestinal bleeding  
20 (37.5%), intracranial haemorrhage (34.4%), muscular hematoma (9.4%), external  
21 haemorrhage (16.9%) and internal haemorrhage (1.9%). At 1 month, 179 patients (19.8%)  
22 died, mostly patients with intracranial haemorrhage (64.2%). Prognostic factors for death  
23 were age and Glasgow coma scale at admission for intracranial haemorrhage, age and mean  
24 arterial pressure at admission for other major haemorrhages. Oral anticoagulant therapy was a  
25 predictor for death in intracranial haemorrhages. Reversal therapy was initiated in only 50.5%  
26 of patients with vitamin K antagonists, without effect on the mortality rate.

27 **Conclusion:** This study shows the magnitude and the severity of antithrombotic-related major  
28 haemorrhage. The high mortality rate supports careful awareness in individual risk benefit  
29 assessment, especially for elderly.

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31 Word count: 237/250

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

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

3  
4 Word count 5,375 /6,000

5  
6 **Introduction**

7  
8 Antithrombotics, i.e. oral and parenteral anticoagulants as well as antiplatelet agents, have  
9 demonstrated significant benefits in preventing venous or arterial thrombotic events,  
10 especially in coronary disease, stroke, atrial fibrillation, venous thromboembolism and  
11 mechanical heart valves [1]. These drugs are commonly prescribed and their long term use is  
12 increasing, particularly in elderly.

13  
14 Bleeding represent the most well-known and feared complications of antithrombotics.  
15 Numerous studies on adverse drug events reported anticoagulants as the first medication class  
16 implicated in haemorrhage and specifically intracranial haemorrhage (ICH) which often  
17 results in substantial morbidity and mortality [2]. Using adverse drug events from a National  
18 Surveillance System, Budnitz et al demonstrated that warfarin and oral antiplatelet agents are  
19 respectively the first and the third medications leading to emergency department and  
20 hospitalization in adults 65 years of age or older [3]. For antiplatelet agents, gastrointestinal  
21 bleeding and intracranial haemorrhage are well known [4-6].

22  
23 Emergency departments are unique to describe antithrombotic-related major haemorrhage.  
24 We report the results of a prospective cohort that aimed to describe antithrombotic-related  
25 major haemorrhage, diagnostic process, clinical and therapeutic management as well as 1-  
26 month outcome.

## 1 **Material and methods**

### 3 *Patient selection and definitions*

5 Patients older than 16 years admitted in the emergency department of our teaching hospital  
6 with antithrombotic-related major haemorrhage were consecutively included between January  
7 1, 2011 and December 31, 2012. Patients were identified through haemorrhagic symptoms at  
8 emergency admission. Computerised requests based on several related-haemorrhagic  
9 diagnostic codes and specific emergency therapies were made every month on electronic  
10 health records. Then, criteria of major bleeding were required and antithrombotic treatment  
11 searched.

13 According to the French National Authority for Health ( Haute Autorité de Santé - HAS) [7],  
14 major bleeding was defined by at least one of the following criteria : hemodynamic instability  
15 (systolic arterial pressure < 90 mmHg or mean arterial pressure < 65 mm Hg), signs of shock,  
16 uncontrollable bleeding, need for transfusions of red cell packs, need for haemostatic  
17 procedure (embolization, endoscopic procedure, surgery), or a life-threatening bleeding such  
18 as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, thoracic bleeding,  
19 compressive muscular hematoma, acute gastrointestinal bleeding. In addition to these criteria,  
20 we considered major bleeding in case of epistaxis if at least two procedures of nasal packing  
21 were needed and in case of hematuria if the bleeding continued during more than 12 hours  
22 despite bladder washing.

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

26 Patients with major bleeding events associated with antithrombotic during hospitalization,  
27 patients with intentional overdose with antithrombotic drugs and patients with multi-trauma  
28 were excluded.

30 For all included patients, the following clinical and biological data were collected from  
31 electronic health record: demographics, medical history, treatments with their indication and  
32 duration, type of bleeding manifestation, vital signs at admission, contributory procedures that  
33 led to diagnostic of major bleeding (CT scan, endoscopy) , biological data on admission,  
34 treatments done in the emergency ward, blood transfusions, specific reversal treatment,  
35 haemostatic procedure, time between admission and diagnosis, time between admission and  
36 reversal therapy, outcomes, length of stay in hospital, and decision about antithrombotic  
37 treatment after the haemorrhagic event. At 1 month, clinical data about hemorrhagic or  
38 ischemic event and vital status were asked.

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

### 42 *Data processing and analysis*

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

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

6  
7 The primary outcome was 1-month mortality.

8  
9 Between subgroups comparisons were performed using student's t test for parametric data,  
10 Mann-Whitney U test for non parametric data, and the chi-square test for qualitative data.  
11 Crude relative risks were estimated along with 95% confidence interval. Prognostic factors for  
12 death at 1-month were defined in the overall population and in the subgroups of patients with  
13 intracranial haemorrhage and patients with other bleeding than intracranial haemorrhage.  
14 Multivariate logistic models were run in subgroups of patients with intracranial haemorrhage  
15 and of patients with other major bleeding to assess the predictors of death. Statistical analysis  
16 was conducted using SAS software version 9.3 (SAS Institute Inc, Cary, NC, USA). A p  
17 value of .05 was considered statistically significant.

18  
19

## 1 **Results**

### 2 3 *Population characteristics*

4  
5 In 2011 and 2012, 98,377 adult patients were admitted in our emergency department. Nine  
6 hundred and thirteen patients (0.9%) with major bleeding while receiving at least one  
7 antithrombotic drug were analysed, which represented 1.2 patients per day. During the study  
8 period, there were no monthly variations. The mean age was  $80 \pm 10$  years ( range : 21-103);  
9 median, 82 years) with a sex ratio of 1.1. Hospitalization was required for 728 patients (79%)  
10 with a mean length of stay of  $8.5 \pm 14.2$  days, including  $1.3 \pm 3.9$  days in intensive care units.

11  
12 Demographic characteristics and indications of antithrombotics, according to the therapeutic  
13 subgroups, are reported in table 1. Among 913 patients, 152 (17.2%) had a combination of  
14 antithrombotic agents. The duration of prescription was unknown in 46.3% of cases.

15 Gastrointestinal bleeding and intracranial haemorrhage (ICH) represented more than 70% of  
16 major haemorrhagic events (table 2). There was a statistically significant association between  
17 types of antithrombotics and types of haemorrhage ( $p < .0001$ ): AP-related haemorrhages  
18 were mostly ICH ( $n = 164$ , 39%) and gastrointestinal bleeding ( $n = 179$ , 42%) whereas OA-  
19 related haemorrhages were mostly external haemorrhages or muscular hematomas ( $n = 147$ ,  
20 34%), gastrointestinal bleeding ( $n = 140$ , 33%) and ICH ( $n = 134$ , 31%).

21 The mechanism of the ICH, known in 307 patients, was traumatic in 44.6% of cases, mostly a  
22 fall from standing height, spontaneous in 45.6%, impossible to determine in 9.4%. In  
23 traumatic ICH, there were more patients with AP than OA (60% versus 40%). Frequencies of  
24 AP and OA were similar in those patients with spontaneous ICH (51.5% versus 48.5%).

### 25 26 *Predictors of 1-month mortality*

27  
28 At 1 month, data from 903 documented medical records were analysed. In this population,  
29 179 patients died at 1 month (19.8 %). Fifty-five patients died in the emergency ward.  
30 Death occurred within the first 3 days of hospitalization in 81 patients. The distribution of  
31 death according to the type of haemorrhagic events showed that intracranial haemorrhage was  
32 responsible of the most number of death (115/179 patients, 64.2%). Among 267 patients with  
33 a known ICH mechanism and a known vital status at 1 month, 1-month mortality was higher  
34 in spontaneous ICH than in traumatic ICH: 45.9% (62/135) vs. 26.5% (35/132),  $p = 0.001$ .  
35 Among 314 patients with ICH, 27 (8.6%) had limitation of life support; 22 patients (7.7%) out  
36 of the 287 remaining patients underwent surgery: 18 out of those 22 patients were alive at one  
37 month (81.8%) compared to 178 out of 265 patients who did not have surgery (67.2%),  $p =$   
38 0.15. Among 342 patients with GI bleeding, 61 had an invasive therapy (endoscopy,  $n = 42$ ;  
39 surgery,  $n = 20$ ; embolisation,  $n = 3$ ; of note 4 patients had two procedures); 59 out of those  
40 61 patients were alive at one month (96.7%) compared to 249 out of 281 patients who did not  
41 have invasive therapy (88.6%),  $p = 0.055$ . One-month mortality was not associated with the  
42 type of antithrombotic agents (table 3).

43 In univariate analysis, prognostic factors for 1-month mortality in case of intracranial  
44 haemorrhage were age, Glasgow coma scale (GCS) score, the type of antithrombotic agents  
45 (OA), time between admission and diagnosis and time between admission and biological  
46 results (table 4). OA was associated with a 1.4-fold increased risk for 1-month mortality  
47 compared to AP: RR = 1.5 (95%CI, 1.1 to 2.0); relative risk for PA compared to AP was 1.2  
48 (95%CI, 0.6 to 2.5). Prognostic factors for 1-month mortality after other haemorrhagic events  
49 were age, mean arterial pressure at admission and type of antithrombotic agents (table 4). PA

1 was associated with a 1.7-fold increased risk for 1-month mortality compared to AP: RR = 1.7  
2 (95%CI, 0.8 to 3.3); relative risk for OA compared to AP was 0.8 (95%CI, 0.5 to 1.4).

3 Adjusting for age and GCS through multivariate logistic regression, OA remained statistically  
4 associated with ICH 1-month mortality compared to AP (p = 0.0451) and PA did not reached  
5 statistical significance for other haemorrhagic event 1-month mortality compared to AP (p =  
6 0.57).

7 Among surviving patients at 1 month (724), antithrombotic treatment was continued without  
8 modifications in 382 patients (52.8%), with modifications in 125 patients (17.3%),  
9 discontinued in 171 patients (23.6%), not determined in 46 patients (6.3%). Antithrombotic  
10 treatment was stopped in all patients with ICH.

### 11 *Oral anticoagulant group: characteristics, clinical and therapeutic management*

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

19 At admission, the international normalized ration (INR) was in the therapeutic range (between  
20 2 and 3) in 41.9% of cases, under the range in 18.6% and above in 39.5%. Median [p25-p75]  
21 INR value was slightly higher among patients with ICH who died within one month compared  
22 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  
23 observed in other type of haemorrhage: 3.7 [2.4-7.4] vs. 2.8 [2.2-4.2] (p = 0.031).

24 Reversal therapy was initiated in only 215 patients (50.5%); the complete recommended  
25 treatment, that is prothrombin complex concentrate (PCC) at a dose equal or superior to 20  
26 IU/kg in association with 5 or 10 mg of vitamin K, was prescribed only in 80 patients  
27 (19.1%). This reversal treatment was not significantly associated with 1-month mortality  
28 considering only patients with no limitation of life support: 5/21 (23.8%) vs. 11/40 (27.5%) in  
29 patients with ICH and 6/70 (8.6%) vs. 7/68 (10.3%) for other type of haemorrhage.

30 Two-hundred and two patients needed blood transfusions (mean 2.3 units of red cells), for  
31 gastrointestinal bleeding in 101 patients, muscular hematomas in 39 patients, epistaxis in 17  
32 patients. Fifty patients required surgery.

33 At 1 month, OA therapy was continued in 53% of cases and stopped in 24% of cases. In 23%  
34 of cases, treatment was changed, switch with antiplatelet agents or stop of combination.

### 35 *Antiplatelet group: characteristics, clinical and therapeutic management*

36 In the antiplatelet group (420 patients), aspirin represented 88% of cases, clopidogrel 20% of  
37 cases, dual therapy 9% of cases. Demographic and clinical characteristics, number of red cell  
38 transfusions, hospitalization rate and mortality rate were not different compared to patients  
39 from the oral anticoagulant group (table 5). No platelet transfusion was prescribed.

40 At 1 month, antiplatelet agents were continued in 61% of cases, discontinued in 24% of cases.  
41 In 15% of cases, the treatment was modified, that is stop of the dual therapy or switch with  
42 other antiplatelet drugs.

### 43 *Parenteral anticoagulant group: characteristics, clinical and therapeutic management*



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

## 1 Discussion

2  
3 With more than one patient per day admitted in our emergency ward on a two-year period, our  
4 study highlighted the magnitude of major bleeding associated with antithrombotics, whatever  
5 the antithrombotic drug.

6  
7 The patient's median age was high (82 years old), reflecting the increasing use of  
8 antithrombotic in elderly in all their indications, as previously reported [4]. Particularly, the  
9 number of patients with atrial fibrillation will progressively increase in the next years.  
10 Consequently, the number of major bleeding will still increase in this frail population, leading  
11 to an important morbidity and mortality. Despite this increased haemorrhagic risk secondary  
12 to age, the elderly still have the most important benefits of antithrombotics, even after a major  
13 bleeding event [8]. In survivors, we observed that 53 % of the oral anticoagulant group and  
14 61% of the antiplatelet group continued the same antithrombotic treatment 1 month after the  
15 haemorrhagic event.

16  
17 In our study, 152 patients were taking more than one antithrombotic drugs with various  
18 combinations. Even if the combination of antithrombotics increase the haemorrhagic risk [9,  
19 10] the various combination would have complicated the analysis of our study population.  
20 Thus, to compare the different antithrombotic agents, we classified our patients in only three  
21 therapeutic groups, considering that the haemorrhagic risk was most important with oral and  
22 parenteral anticoagulants than with antiplatelet agents [1, 11]. We identified 64 patients with  
23 major bleeding associated with parenteral anticoagulant, especially heparins and  
24 fondaparinux. To our knowledge, this was the first report on major bleeding in an ambulatory  
25 population with these antithrombotics. Usually, most data came from multicenter clinical trial  
26 [13]. Our results showed that the corresponding population was different from patients of  
27 others therapeutic groups, i.e. more severity, increased mortality rate in patients with mainly  
28 venous thromboembolic indication. In this group, the distribution of the different  
29 haemorrhagic complications was equivalent to other group of antithrombotics, as previously  
30 reported [14].

31  
32 In the therapeutic management of the hemorrhagic events, there were an important number of  
33 blood transfusions, with numerous haemostatic procedures (surgery, endoscopic procedure).  
34 Indications of blood transfusions were left to physician appreciation. In the oral anticoagulant  
35 group, reversal therapy was used in only 50.5 % of cases, despite the national guidelines [7].  
36 In ICH associated with oral anticoagulant, reversal therapy with PCC and vitamin K was  
37 specially used because of the poor prognosis of this bleeding event. Nevertheless, the  
38 mortality rate was not different with or without reversal therapy in case of ICH. In the  
39 antiplatelet group, no platelet transfusion was needed, according to the recent systematic  
40 review in traumatic and spontaneous ICH [15].

41  
42 Gastrointestinal bleeding was the first major haemorrhagic events in our study, with a similar  
43 number associated with OA and AP. Even if this bleeding risk was well known, international  
44 trial and meta-analysis have reported various risk levels according to the antithrombotic  
45 drugs. Relative risk of gastrointestinal risk was estimated at 1.8 and 1.6 for respectively  
46 aspirin and clopidogrel, two-fold higher for oral anticoagulant therapy, especially when the  
47 INR value is high [5, 16, 17]. In our OA group, INR value was not a prognostic factor.  
48 Dangerous combinations such as OA + AP or dual antiplatelet therapy induced a more 2-fold  
49 higher risk of gastrointestinal bleeding [10, 12].

1 In 314 patients (34.4 %), the haemorrhagic event was intracranial, spontaneous or traumatic,  
2 leading to a dramatic prognosis (64.2% of dead patients at 1 month had IHC). The number of  
3 patients with OA and AP was similar, but, the multivariate OR for death in ICH patients was  
4 significantly unfavourable at one month in OA versus AP (OR = 1.89 (95%CI 1.01-3.54).  
5 This high mortality has been reported elsewhere [18, 19] and seemed to be dependant to the  
6 mechanism of the ICH and to the antithrombotic medication. In a multicenter Italian study in  
7 emergency departments, Baldi and al reported a mortality rate of 44% in post traumatic IHC  
8 (41% with AP and 51% with OA), and 58% in spontaneous ICH (51% with AP and 69% with  
9 OA [4]. Like others, we found that age and Glasgow coma scale will be strong prognostic  
10 factors in patients with intracranial haemorrhage. In case of ICH, time between admission and  
11 diagnosis and time between admission and first biological results were significantly shorter in  
12 patients who died, which could be explained by a more severe condition on admission.  
13 In head trauma, oral anticoagulant led to 10-fold higher incidence of intracranial  
14 haemorrhagic lesions (3 versus 29%), reaching a mortality rate near to 60% [20]. Old age  
15 increased furthermore this rate (OR = 1.2 for each increase of 10 years) [21]. As reported by  
16 Dowlatshahi et al [22] and as shown in our results, the mortality did not seem to be affected  
17 by complete reversal therapy.

18  
19 For antiplatelet drugs, there is a great heterogeneity for establishing a strong link between  
20 ICH and this medication, because of various inclusion criteria, different methodology,  
21 severity at inclusion, mechanism, outcomes. Nevertheless, antiplatelet drugs appeared to be a  
22 risk factor for IHC in patients with minor head trauma. In a recent meta-analysis, Bachelor et  
23 al [23] reported an important overall relative risk of aspirin in all head trauma (OR = 2.43),  
24 higher than clopidogrel (OR = 1.55); other studies have reported opposite results, with a more  
25 important risk with clopidogrel than with aspirin [24, 25]. Whatever these various risk  
26 assessments, the old age and the Glasgow coma score appeared to be strong prognosis factors,  
27 as shown in our results [26]. In spontaneous ICH, the systematic review of Thompson et al  
28 reported an increase of mortality rate induced by antiplatelet agents (40% in univariate  
29 analysis, 27% in multivariate analysis) and a higher poor prognosis (respectively 29 and 10%)  
30 [27].

### 31 32 **Strengths**

33  
34 The selection method used in our study would have contributed to increase the number of  
35 haemorrhagic events. We selected patients firstly from the haemorrhagic symptom at  
36 emergency admission, in contrast with most studies on this subject which screened patients  
37 from the medication. Our method was quite similar with the study reported by Budnitz et al,  
38 in which coders reviewed clinical records of each emergency department visit to identify  
39 adverse drug events [3]. Heterogeneity of codes compelled to use a list of about forty different  
40 diagnostic codes relative to haemorrhagic events and pathologies. This first step was then  
41 completed by the search for the criteria of major bleeding and finally by the identification of  
42 the antithrombotic medication, information often missed in the emergency medical record.  
43 This method could explain the equal number of major bleeding with oral anticoagulant and  
44 antiplatelet drugs, with a quite equivalent distribution of types of haemorrhage, particularly  
45 intracranial haemorrhage and gastrointestinal bleeding. In the same way, it could explain the  
46 relative important group of patients with parenteral anticoagulants.

### 47 48 **Limitations**

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

## 15 **Conclusion**

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

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**Table 1** Demographics and clinical characteristics.

<b>Patients</b>	<b>n</b>	<b>%</b>
<b>Gender</b>		
Male	480	52.6
Female	433	47.4
<b>Age, years</b>		
21 – 60	44	4.8
61 – 70	83	9
71 – 80	260	28.5
81 – 103	526	57.6
<b>Indication of antithrombotics</b>		
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
<b>Duration of antithrombotic medication</b>		
< 1 year	117	12.8
1 > years > 5	158	17.3
> 5 years	215	23.6
Unknown	423	46.3
<b>Type of antithrombotic agents</b>		
Oral anticoagulant	429	47.0
Vitamin K antagonist	427	46.8
<i>alone</i>	353	
<i>in combination with antiplatelet</i>	61	
<i>other combination</i>	12	
New oral anticoagulant	2	0.2
Antiplatelet agents	420	46.0
<i>alone</i>	380	
<i>dual therapy</i>	39	
Parenteral anticoagulant	64	7.0
<i>Unfractionned heparin</i>	5	
<i>Low molecular weight heparin</i>	43	
<i>Fondaparinux</i>	15	
<i>Danaparoid</i>	1	

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**Table 2** Distribution of haemorrhagic events

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

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

	Dead patients N = 179	Alive patients N = 724	
<b>Haemorrhagic event</b>	<b>n (%)</b>	<b>n (%)</b>	<b>&lt; 0.0001</b>
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)	
<b>Treatment group</b>			<b>0.5592</b>
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;

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

**B**

Characteristic	Died patients N = 64	Alive patients N = 525	
<b>Treatment</b>			<b>0.1561</b>
OA	27 (42.2)	261 (49.7)	
AP	28 (43.7)	225 (42.8)	
PA	9 (14.1)	39 (7.46)	
<b>Clinical characteristics</b>			
Female	29 (45.3)	236 (44.9)	0.9564
Age, years	83.2 ± 9.2	79.7 ± 10.5	<b>0.0024</b>
Hemoglobin level, g/dL	8.7 ± 2.2	8.8 ± 2.3	0.7662
Mean arterial pressure (mm Hg)	70 ± 19	78 ± 16	<b>0.0034</b>
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

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**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	202 (47.1)	197 (46.9)	36 (56.2)	
Number of units (mean)	2.3	2.0	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)	

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