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## Management of major bleeding outcomes under antithrombotic therapy in real-life

*F. Moustafa*<sup>1,2</sup>, *A. Corriger*<sup>1,2</sup>, *C. Lambert*<sup>3</sup>, *A Barres*<sup>4</sup>, *C. Camminada*<sup>1</sup>, *D Teissandier*<sup>1</sup>, *J Saint-Denis*<sup>1</sup>, *F Dutheil*<sup>1,2,5,6</sup>, and *J. Schmidt*<sup>1,2</sup>

<sup>1</sup> Department of Emergency. Clermont-Ferrand University Hospital. Clermont-Ferrand. France

<sup>2</sup> Université Clermont Auvergne, F-63000 Clermont-Ferrand, France

<sup>3</sup> Biostatistics Unit, DRCI, Clermont-Ferrand University Hospital. Clermont-Ferrand. France

<sup>4</sup> Department of Medical Information, University Hospital of Clermont-Ferrand, Clermont-Ferrand, France

<sup>5</sup> School of Exercise Science, Australian Catholic University, Melbourne, VIC, Australia

<sup>6</sup> UMR CNRS 6024, “Physiological and psychosocial stress” team, LAPSCO, Clermont-Ferrand, France

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### Corresponding author:

**Farès Moustafa**, Service des urgences, Hôpital Gabriel Montpied,  
58 rue Montalembert, F-63003 Clermont-Ferrand Cedex 1, FRANCE

**Email address** : [fmoustafa@chu-clermontferrand.fr](mailto:fmoustafa@chu-clermontferrand.fr)

**Phone number**: +33 (0)624366369

### Authors' correspondance:

Alexandrine Corriger: [alexandrine.corriger@gmail.com](mailto:alexandrine.corriger@gmail.com)

Céline Lambert : [clambert@chu-clermontferrand.fr](mailto:clambert@chu-clermontferrand.fr)

Alain Barres: [abarres@chu-clermontferrand.fr](mailto:abarres@chu-clermontferrand.fr)

Jennifer Saint-Denis : [jsaintdenis@chu-clermontferrand.fr](mailto:jsaintdenis@chu-clermontferrand.fr)

Christelle Camminada : [ccamminada@chu-clermontferrand.fr](mailto:ccamminada@chu-clermontferrand.fr)

Dorian Teissandier : [dteissandier@chu-clermontferrand.fr](mailto:dteissandier@chu-clermontferrand.fr)

Frédéric Dutheil : [fdutheil@chu-clermontferrand.fr](mailto:fdutheil@chu-clermontferrand.fr)

Jeannot Schmidt : [jschmidt@chu-clermontferrand.fr](mailto:jschmidt@chu-clermontferrand.fr)

**Dear Editors,**

Bleeding is the most serious undesirable event of antithrombotic therapy, though this treatment has shown benefits in terms of venous or arterial thrombosis prevention, particularly in case of atrial fibrillation, stroke, venous thromboembolism, and coronary disease.

Vitamin K antagonists (VKAs) are the most-commonly used anticoagulant treatments. The incidence of major bleedings due to VKAs has been estimated at 7% and that of fatal bleedings at 1%.[1] In randomized clinical trials and real-world experience, direct oral anticoagulants (DOACs) have shown non-inferiority efficacy and a lower incidence of intracranial bleeding than VKAs. Moreover, DOAC and antiplatelet (AP) drugs are similarly implicated in bleeding adverse events.[2] Low-molecular-weight heparin (LMWH) has become a standard treatment for venous-thromboembolism (VTE) prevention, particularly in patients with cancer, but with a major bleeding rates under fondaparinux significantly higher than under enoxaparin.[3]

However, major bleeding in real-life, as well as its management and outcomes, has not yet been thoroughly compared among different antithrombotic treatments. In the current study, we sought to assess the frequency, severity, current management, and outcomes of major bleedings depending on the antithrombotic agent's use in a real-life setting.

We conducted a monocenter, retrospective study based on collected data from consecutive patients enrolled in the RATED registry (NCT02706080) from January 2014 to December 2015. In addition, we employed the pharmacological prescription of reversal therapy or blood transfusion, in an effort to avoid missing major bleeding cases. For this study, only patients over 18 years of age and with major bleeding were considered. According to the French Health Authorities, major bleeding was defined by at least one of the following criteria being present: uncontrollable external bleeding; hemodynamic instability (systolic blood pressure <90mmHg, mean arterial pressure <65mmHg, or signs of shock); requirement for urgent

hemostatic procedure (surgery, embolization, or endoscopy); need for blood transfusion; life-threatening bleeding or functional location (intracranial, intra-spinal, intraocular, retroperitoneal, pericardial, thoracic, acute gastrointestinal, muscular hematoma, or hemarthrosis).[4] The patients, or their legal power of attorney, were informed of the possibility of their personal data being used. The analysis protocol was approved by The French Research Ethics Committee (CPP Sud-Est VI, IRB number: 00008526 – 2013/CE37).

The following parameters were routinely recorded into the RATED registry based on electronic health records: the patient's baseline characteristics; clinical status including any coexisting or underlying conditions; bleeding risk factor; CT scan or echography use; laboratory data at baseline; antithrombotic treatment (indication, duration, drug type, and doses); concomitant drugs; bleeding management (blood transfusion, reversal treatment, or hemostatic procedure), length of hospital stay; and outcomes during hospitalization at 1 and 6 months.

This study sought to describe the characteristics of patients using antithrombotic drugs admitted to the emergency room for major bleeding and to assess both their initial management and outcomes. The major outcome concerned the following: re-bleeding rate, new hospitalization, or death occurring upon hospitalization, or at 1 and 6 months.

All analyses were performed using the Stata software (Version 13, StataCorp, College Station, US). Descriptive statistics were applied for the population, expressed in terms of frequencies and percentages for categorical variables, as well as means and standard-deviations or medians and interquartile ranges for quantitative parameters, depending on statistical distribution (Shapiro-Wilk test for normality study).

From January 2014 to December 2015, 436 patients with major bleeding related to an antithrombotic agent were admitted to the emergency department. Of these, 204 (47%) were under VKA, 167 (38%) under AP, 29 (7%) under DOAC, and 36 (8%) under parenteral anticoagulant.

Major bleeding occurred at the same mean age, regardless of the antithrombotic therapy (**Table 1**). Overall, 191 (44%) patients experienced gastrointestinal bleeding, 59 (13.5%) intracranial bleeding, and 36 (8.25%) muscular hematoma. Patients under VKA were more likely to suffer from muscular hematoma than those under AP, though they were not significantly more likely to suffer from muscular hematoma than those under DOAC or parenteral anticoagulant. Patients under AP were more likely to experience intracranial bleeding than those under either DOAC or parenteral anticoagulant. Major bleeding in patients given DOAC was more likely to consist of gastrointestinal bleeding than bleeding under VKA. Half of the patients with major bleeding under VKA received prothrombin complex concentrate (PCC), either alone or with vitamin K, whereas only 11 out of 29 (38%) with major bleeding under DOAC received PCC or another procoagulant agent. Interestingly, patients under AP were more likely to receive platelet transfusion than those under VKA. Unexpectedly, none of the patients under the parenteral anticoagulant received reversal therapy with protamine sulfate. Definitive discontinuation was two-fold higher for patients under AP or DOAC than those under VKA (12.6% and 13% vs. 6.6%, respectively). However, the clinicians were more likely to maintain the treatment for those under AP than for those under either VKA or DOAC. Moreover, the clinicians were less likely to change the dosing for major bleeding occurring under AP versus VKA, DOAC, or parenteral anticoagulant.

The mortality and re-bleeding rates were 12.9% and 0.0% initially, 4.5% and 12.5% at 1 month, and 5.3% and 10.8% at 6 months, respectively (**Figure 1**). Nevertheless, there was no difference between the antithrombotic agents used in regard to overall mortality. At 1 month, re-bleeding was not significantly higher for patients under VKA than for those under DOAC or parenteral anticoagulant; the overall cause of death was four-fold higher for those under parenteral anticoagulant versus other antithrombotic agents. Unexpectedly, at 6 months, re-bleeding was higher for patients receiving DOAC in comparison to VKA patients.

Our study demonstrated that over a 3-year period, the risk of severe bleeding for patients using antithrombotic agents admitted to the emergency unit was 3.58%, with an estimated risk of 1.89% under VKA and 0.20% under DOAC. Following a bleeding event, the risk of re-bleeding was higher in patients using VKA or AP as compared to those on DOAC or parenteral anticoagulant, with an increased risk of death being observed for the latter.

The observation of fewer major bleedings with DOAC was consistent with the results of previous randomized trials involving all DOACs. The biological plausibility of this favorable association appears to be based on the lower suppression of thrombin generation with DOACs versus warfarin.[5]

Our study revealed a high mortality rate (12.9%) related to the antithrombotic agents employed at initiation. However, about half of the patients received pharmacological treatment designed to antagonize VKA, whereas only one-third received treatment to antagonize DOAC. Though it is yet unclear whether aggressive pro-hemostatic treatment would reduce the mortality rate, current guidelines recommend a clear step-up strategy of transfusion and pro-hemostatic treatment in the case of major bleeding.[6]

We found that the bleeding recurrence rates at 1 month ranged from 4.2% to 13.6% and from 8.1% to 20% at 6 months, depending on the type of antithrombotic agent. Interestingly, over the 3 years, DOAC patients had less bleeding recurrence at 1 month than VKA patients (8.7% vs. 13.6%, respectively) but, instead, more bleeding recurrence at 6 months (20% vs. 11.9%, respectively). Very few studies have focused on bleeding recurrence in patients upon antithrombotic agents. One study showed that the rate of bleeding recurrence for patients with gastrointestinal bleeding was 19% over the 1-year follow-up.[7] In another study, which looked at patients undergoing antithrombotic therapy for atrial fibrillation (AF) and gastrointestinal bleeding, 17.7% experienced severe bleeding recurrence, and 12.1% gastrointestinal bleeding over the 2-year follow-up.[8]

This cohort study is one of the first studies in France to analyze the incidence of severe hemorrhage and bleeding recurrences in patients on antithrombotic therapy admitted to an emergency department. The study has, however, several limitations that must be mentioned. First, due to the observational study design, the data are only hypothesis-generating, potentially providing a useful basis for future controlled clinical trials. Secondly, the patients were recruited in a single center, which is likely to generate less reproducibility, in spite of avoiding any practice variability among different centers. Thirdly, there is no external adjudication of the major bleeding events, which were generated using recorded data to fit with the French definition of major bleeding. However, prior studies have shown that adjudicated data usually match well with onsite outcome assessments.[9,10] Another study limitation is that the patient numbers were rather small, and the robustness of the findings should, therefore, be questioned. The main study strength is that the population-based sample properly describes the management and time course of major bleeding in a “real-world” clinical care setting, as opposed to a protocol-driven randomized trial. Consequently, the generalizability of the findings appears to be enhanced.

In summary, the mortality rate in patients presenting with major bleeding during antithrombotic therapy proves to be high. In spite of the high risk of fatal bleeding, only half of the patients receive transfusion or prohemostatic treatment. Moreover, the rate of bleeding recurrence proves to be similarly high, with a higher risk of bleeding recurrence at 1 month for VKA and at 6 months for DOAC patients. Better implementation of reversal protocols in clinical practice is deemed necessary to improve the quality of care for these vulnerable patients who require accurate follow-up up to 6 months following a major bleeding event.

### **Competing interests**

Dr. Moustafa has served as a consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim and Sanofi, been a speaker for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Daiichi-Sankyo and Sanofi, and received grants from Sanofi, Bayer HealthCare, Roche diagnosis and LFB.

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### **Authors' contributions**

FM and AC designed the study, performed the measurements, analyzed the data, prepared the figures, and drafted the manuscript.

CL contributed to the manuscript's statistical analysis.

AB, JSD, CC, DT, FD, and JS contributed to the study design, discussed the findings, and revised the manuscript.

All authors have read and approved the final manuscript.

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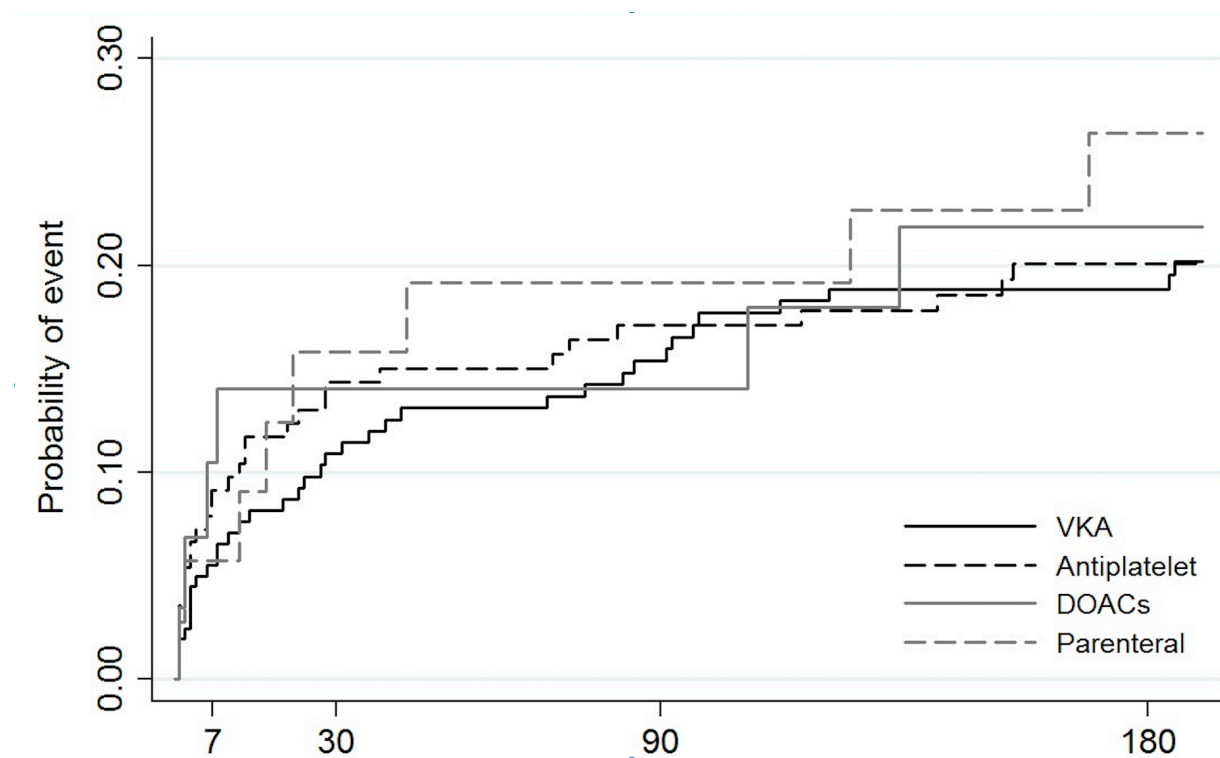
**Table 1. Clinical characteristics of patients with major bleeding depending on the antithrombotic agent used**

	VKA (n=204)	Antiplatelet (n=167)	DOACs (n=29)	Parenteral (n=36)
<b>Clinical characteristics</b>				
Age (years)	78.7 ± 11.8	78.9 ± 11.2	78.8 ± 8.1	75.7 ± 15.8
Gender (male)	105 (51.5)	99/166 (59.6)	18 (62.1)	18 (50.0)
<b>Indication</b>				
VTE	29 (14.2)	4 (2.4)	5 (17.2)	14 (38.9)
AF	99 (48.5)	19 (11.4)	11 (37.9)	3 (8.3)
Stroke	2 (1.0)	16 (9.6)	1 (3.4)	1 (2.8)
Myocardial infarction	2 (1.0)	11 (6.6)	0 (0.0)	0 (0.0)
Peripheral arterial disease	2 (1.0)	18 (10.8)	2 (6.9)	0 (0.0)
Mechanical heart valve	14 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Others	10 (4.9)	23 (13.8)	1 (3.4)	6 (16.7)
Unknown	46 (22.5)	76 (45.5)	9 (31.0)	12 (33.3)
<b>Bleeding site</b>				
Gastrointestinal	77 (37.7)	83 (49.7)	15 (51.7)	16 (44.4)
Intracranial	24 (11.8)	31 (18.6)	1 (3.4)	3 (8.3)
Muscular hematoma	29 (14.2)	2 (1.2)	2 (6.9)	3 (8.3)
Hematuria	12 (5.9)	8 (4.8)	2 (6.9)	3 (8.3)
Epistaxis	14 (6.9)	4 (2.4)	1 (3.4)	0
External bleeding <sup>1</sup>	4 (2.0)	2 (1.2)	0	0
Others	44 (21.6)	37 (22.2)	8 (27.6)	11 (30.6)
<b>Bleeding Management</b>				
PCC	112 (54.9)	3 (1.8)	5 (17.2)	2 (5.6)
Other procoagulant	1 (0.5)	3 (1.8)	6 (20.7)	0
Vitamin K	147 (72.1)	1 (0.6)	1 (3.4)	2 (5.6)
Vitamin K and PCC	107 (52.5)	1 (0.6)	1 (3.4)	2 (5.6)
Protamine sulfate	2 (1.0)	1 (0.6)	0	0
Surgery	16 (7.8)	11 (6.6)	1 (3.4)	4 (11.1)
Endoscopy	33 (16.2)	39 (23.4)	9 (31.0)	6 (16.7)
Embolization	3 (1.5)	2 (1.2)	0	2 (5.6)
Fresh frozen plasma	14 (6.9)	12 (7.2)	1 (3.4)	2 (5.6)
Number of units	1.5 ± 0.8	1.8 ± 1.5	1.0±0.0	2.0 ± 0.0
Blood transfusion	89 (43.6)	64 (38.3)	8 (27.6)	15 (41.7)
Number of units	2.5 ± 1.2	2.3 ± 1.6	2.6 ± 1.2	2.3 ± 1.5
Platelet transfusion	1 (0.5)	9 (5.4)	0	0
<b>Antithrombotic</b>				
Stopped definitively	11/167 (6.6)	15/119 (12.6)	3/23 (13.0)	1/26 (3.8)
Stopped temporarily	87/167 (52.1)	50/119 (42.0)	12/23 (52.2)	9/26 (34.6)
Maintained	19/167 (11.4)	41/119 (34.5)	2/23 (8.7)	6/26 (23.1)
Changed dose	50/167 (29.9)	13/119 (10.9)	6/23 (26.1)	10/26 (38.5)
<b>Initial outcomes</b>				
All death	23/180 (12.8)	20/144 (13.9)	3/26 (11.5)	3/29 (10.3)
Fatal bleeding	5/180 (2.8)	7/144 (4.9)	2/26 (7.7)	2/29 (6.9)
Hospitalization (acute care)	187 (91.7)	144 (86.2)	27 (93.1)	30 (83.3)
Days of hospitalization	8 [4; 13]	6 [3; 12]	8 [4; 13]	6 [2; 14]
<b>1 month outcomes</b>				
All death	6/180 (3.3)	6/144 (4.2)	1/26 (3.8)	4/29 (13.8)
Fatal bleeding	0/180 (0.0)	0/144 (0.0)	0/26 (0.0)	0/29 (0.0)
Re-bleeding	22/162 (13.6)	17/125 (13.6)	2/23 (8.7)	1/24 (4.2)
Re-hospitalization	16/162 (9.9)	13/125 (10.4)	2/23 (8.7)	1/24 (4.2)
<b>6 months outcomes</b>				
All death	11/180 (6.1)	6/144 (4.2)	2/26 (7.7)	1/29 (3.4)
Fatal bleeding	0/180 (0.0)	1/144 (0.7)	1/26 (3.8)	0/29 (0.0)
Re-bleeding	17/143 (11.9)	9/111 (8.1)	4/20 (20.0)	2/21 (9.5)
Re-hospitalization	12/143 (8.4)	7/111 (6.3)	3/20 (15.0)	2/21 (9.5)

*Data are presented as frequencies (percentages), as mean  $\pm$  standard deviation or as median [interquartile range].  
Abbreviations: Parenteral (LMWH, Fonda, UFH); VTE: venous thromboembolism; AF: atrial fibrillation; VKA: vitamin K antagonist; DOAC: direct oral anticoagulant; NSAID: non-steroidal anti-inflammatory drugs, PCC prothrombin complex concentrate*

<sup>1</sup> Scalp injury, vascular injury, hemoptysis.

**Figure 1. Cumulative rate of death according to the antithrombotic agent used (survival analysis)**



<i>Days of Death, Patient at risk</i>	<b>7</b>	<b>30</b>	<b>90</b>	<b>180</b>
<b>VKA (N=204)</b>	182	162	148	130
<b>Antiplatelet (N=167)</b>	145	128	118	105
<b>DOACs (N=29)</b>	25	22	22	20
<b>Parenteral (N=36)</b>	28	25	24	19

*VKA: vitamin K antagonist; DOAC: direct oral anticoagulant*