

# Management of Severe Bleeding in Patients Treated with Direct Oral Anticoagulants

## *An Observational Registry Analysis*

Pierre Albaladejo, M.D., Ph.D., Charles-Marc Samama, M.D., Ph.D., F.C.C.P., Pierre Sié, M.D., Ph.D., Sophie Kauffmann, M.D., Vincent Mémier, M.D., Pierre Suchon, M.D., Ph.D., Alain Viallon, M.D., Ph.D., Jean Stéphane David, M.D., Ph.D., Yves Gruel, M.D., Ph.D., Lorenn Bellamy, M.D., Emmanuel de Maistre, M.D., Ph.D., Pauline Romegoux, B.Sc., Sophie Thoret, Ph.D., Gilles Pernod, M.D., Ph.D., Jean-Luc Bosson, M.D., Ph.D., on behalf of the GIHP-NACO Study Group\*



This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

### ABSTRACT

**Background:** The use of prothrombin complex concentrates and the role of plasma concentration of anticoagulants in the management of bleeding in patients treated with direct oral anticoagulants are still debated. Our aim was to describe management strategies and outcomes of severe bleeding events in patients treated with direct oral anticoagulants.

**Methods:** We performed a prospective cohort study of 732 patients treated with dabigatran, rivaroxaban, or apixaban hospitalized for severe bleeding, included prospectively in the registry from June 2013 to November 2015.

**Results:** Bleeding was gastrointestinal or intracranial in 37% (212 of 732) and 24% (141 of 732) of the cases, respectively. Creatinine clearance was lower than 60 ml/min in 61% (449 of 732) of the cases. The plasma concentration of direct oral anticoagulants was determined in 62% (452 of 732) of the cases and was lower than 50 ng/ml or higher than 400 ng/ml in 9.2% (41 of 452) and in 6.6% (30 of 452) of the cases, respectively. Activated or nonactivated prothrombin complex concentrates were administered in 38% of the cases (281 of 732). Mortality by day 30 was 14% (95% CI, 11 to 16).

**Conclusions:** Management of severe bleeding in patients treated with direct oral anticoagulants appears to be complex. The use of prothrombin complex concentrates differs depending on bleeding sites and direct oral anticoagulant plasma concentrations. Mortality differs according to bleeding sites and was similar to previous estimates. (ANESTHESIOLOGY 2017; 127:111-20)

**D**IRECT oral anticoagulants (DOACs), anti-IIa (dabigatran) or anti-Xa (rivaroxaban, apixaban, and edoxaban), are now recognized as a major step forward for patients with nonvalvular atrial fibrillation or recurrent venous thromboembolism requiring long-term anticoagulation for the prevention of thromboembolic events. The efficacy–safety ratio of DOACs is similar or even better in comparison with vitamin K antagonists (VKA) in clinical trials,<sup>1,2</sup> and this benefit appears to be reproduced in the real world,<sup>3</sup> especially with the reduction of approximately one half of intracranial hemorrhages compared with VKA. However, spontaneous severe bleeding still occurs at significant rates during DOAC treatment. Based on the reported experience of severe bleeding in clinical trials,<sup>4–6</sup> a limited number of case reports, and conflicting results of prothrombin complex concentrates (PCCs) and activated PCCs in animal studies or *in vitro* or *ex vivo* studies in humans,<sup>7–10</sup>

### What We Already Know about This Topic

- Specific reversal strategies are currently available for dabigatran and in development for the anti-Xa agents. Other strategies used to manage bleeding in patients treated with these direct oral anticoagulants include measuring plasma levels of anticoagulants and therapy with prothrombin complex concentrates. However, there is little information currently available regarding these management modalities.

### What This Article Tells Us That Is New

- In a prospective cohort registry study of 732 patients treated with direct oral anticoagulants and hospitalized for severe bleeding, bleeding sites were gastrointestinal in 37% and intracranial in 24% of the cases. Activated or nonactivated prothrombin complex concentrates were administered in 38% of the cases with a day 30 mortality of 13.5% and varied according to bleeding sites but was similar to previous reports. This report provides a detailed assessment of direct oral anticoagulant-treated patients managed in clinical settings.

This is a Coagulation 2016 article.

Submitted for publication July 28, 2016. Accepted for publication February 23, 2017. From the Department of Anesthesiology and Intensive Care Medicine, Grenoble-Alpes University Hospital, Grenoble, France (P.A.); Department of Anesthesiology and Intensive Care Medicine, Assistance Publique-Hôpitaux de Paris, Cochin University Hospital, Paris Descartes University, Paris, France (C.-M.S.); Department of Hematology, Toulouse University Hospital, Toulouse, France (P. Sié, V.M.); Department of Anesthesiology and Intensive Care Medicine, Clermont-Ferrand University Hospital, Clermont-Ferrand, France (S.K.); Laboratory of Hematology, La Timone Hospital; INSERM, UMR\_S 1062, Nutrition Obesity and Risk of Thrombosis; Nutrition Obesity and Risk of Thrombosis, Aix-Marseille University, UMR\_S 1062, Marseille, Copyright © 2017, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2017; 127:111-20

guidelines to manage bleeding in patients treated with DOACs have been published.<sup>11,12</sup> Owing to the lack of clinical trials until the recent introduction of specific antidotes of dabigatran (idarucizumab<sup>13</sup>) or xabans (andexanet alfa<sup>14</sup>), these guidelines mainly reflect expert opinions and have a low evidence level.

To obtain more data on the current management of these patients, we set up a large multicenter prospective observational study on a European binational basis. The present article reports the results obtained in 732 patients with major bleeding requiring hospitalization when specific antidotes were not available. The primary objective of the study was to describe the management of bleeding episodes and subsequent outcomes until day 30. The secondary objectives were to describe the typology of bleeding, to describe the clinical and biologic characteristics of the patients on admission, and to analyze how these data have influenced the choice of treatment, in particular the use of reversal agents (four-factor PCC or activated PCC).

## Materials and Methods

The GIHP-NACO registry (NCT02185027) (Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux) is a large, prospective, multicenter registry, set up by the Groupe d'Intérêt en Hémostase Périgéographique (GIHP), enrolling patients treated with a DOAC and hospitalized for spontaneous or posttraumatic bleeding or who needed urgent invasive procedures (for a list of participating centers, see the appendix) in 36 centers in university, general, and private hospitals in France and Belgium (www.ClinicalTrials.gov Identifier NCT02185027). The registry opened in June 2013 and closed in November 2015. A subsample of these data was presented at the American Society of Hematology Meeting in San Francisco, California, in 2014 and published as an abstract (*Blood* 2014; 124:2877). This report presents the data from patients with severe bleeding under treatment with DOACs (dabigatran, rivaroxaban, or apixaban) for indications including atrial fibrillation and treatment of deep venous thrombosis or pulmonary embolism. Patients treated with DOACs for prevention of venous thromboembolism after major orthopedic surgery were not included. The institutional review board (Comité d'Éthique des Centres d'Investigation Clinique de l'Inter-région

Rhône-Alpes-Auvergne, France; institutional review board number 5891) approved the study (reference 2013-02). Oral consent was obtained from all patients or proxies. Written informed consent of the patients was not necessary according to French law regarding observational studies.

Local investigators screened hospitalized patients presenting with bleeding events. Data including demographic, clinical, laboratory tests, and treatment were documented using an electronic case report form providing immediate and continuous monitoring for completeness and accuracy (ClinInfo S.A., France).

Bleeding management was assessed by collecting the following: rates and counts of erythrocyte, plasma or platelet transfusions, the use of agents such as PCC, factor VIII inhibitor bypass activator (FEIBA®, France), recombinant activated factor VII concentrate, fibrinogen concentrates, or tranexamic acid. Three-factor PCCs were not available in the participating centers. In France, three four-factor PCCs with similar contents in factors II, VII, IX, and X and proteins C and S were used: KANOKAD® (LFB, Les Ulis, France), OCTAPLEX® (Octapharma, Boulogne-Billancourt, France), and CONFIDEX® (CSL-Behring, Marburg, Germany).<sup>15,16</sup>

## Clinical Outcome Definitions

All clinical outcomes were assessed 30 days after admission. All bleeding events were classified as major or nonmajor clinically relevant.

Major bleeding was defined as overt bleeding with any of the following: fatal bleeding and/or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 20 g/l or more or leading to transfusion of two or more units of whole blood or red cells.<sup>17</sup>

Since all patients included in this cohort were admitted to a hospital, nonmajor bleeding fulfilled nonmajor clinically relevant criteria defined as any sign or symptom of hemorrhage that did not fit the criteria for the International Society of Thrombosis and Hemostasis (ISTH) definition of major bleeding but did meet at least one of the following criteria: (1) requiring medical intervention by a healthcare professional; (2) leading to hospitalization or increased level of care; or (3) prompting a face-to-face (*i.e.*, not just a telephone or electronic communication) evaluation.<sup>18</sup>

On day 30 postbleeding, patients were also evaluated for suspected major cerebral and cardiovascular events (MACCEs) after the acute bleeding event. MACCEs were defined as fatal or nonfatal cardiovascular complication events as follows: acute coronary syndrome, stroke or transient ischemic attack or systemic embolism, deep venous thrombosis or pulmonary embolism, pulmonary edema, cardiogenic shock, or any other fatal cardiovascular event as assessed by investigators. It excluded rebleeding or any new bleeding episode. The fatality rate was assessed at day 30 postbleeding.

France (P. Suchon); Department of Emergency Medicine, Saint Etienne University Hospital, Saint Etienne, France (A.V.); Department of Anesthesiology and Intensive Care Medicine, Hospices Civils de Lyon, Lyon Sud University Hospital, Pierre Benite, France (J.S.D.); Department of Hematology, Tours University Hospital, Tours, France (Y.G.); Department of Anesthesiology and Intensive Care Medicine, Brest University Hospital, Brest, France (L.B.); Department of Hematology, Dijon University Hospital, Dijon, France (E.d.M.); and Center of Clinical Investigation (P.R., J.-L.B.), Biostatistic Unit (S.T.), and Department of Vascular Medicine (G.P.), Grenoble Alpes University Hospital, Techniques pour l'Évaluation et la Modélisation des Actions de Santé (ThEMAS), Techniques de l'Ingénierie Médicale et de la Complexité (TIMC), Unité Mixte de Recherche (UMR), CNRS 5525, Université Grenoble-Alpes, Grenoble, France.

\*Members of the Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux (GIHP-NACO) Study Group are listed in the appendix.

### Statistical Analysis

Descriptive results are expressed as frequency and percentage for categorical variables and were compared using the chi-square test (or Fisher exact test for small samples).  $P < 0.05$  was considered significant. For continuous variables, statistics are expressed as median, range, interquartile range, and 95% CIs (V.13.0; Stata Corp, USA).

### Results

From June 2013 to November 2015, 732 patients treated with DOACs and admitted to 36 hospitals were consecutively included in the registry. Eligible patients were identified from different departments: emergency rooms, intensive care units, and the departments of neurology, cardiology, gastroenterology, and surgery. There were 535 patients (73%) admitted to the hospital from the emergency room, and 156 (21%) and 39 (5.3%) were admitted directly to intensive care units or to other medical or surgical departments, respectively.

The demographic and clinical characteristics of the patients are presented in table 1. Among the patients included in this analysis, 207 (28%) were treated with dabigatran, 472 (64%) were treated with rivaroxaban, and 53 (7.2%) were treated with apixaban. When patients were treated with rivaroxaban (10 mg) or dabigatran (75 mg twice daily; unlicensed therapeutic protocols in Europe for atrial fibrillation or venous thromboembolism treatment), the indication was confirmed with the local investigator. As a result, 85% of the patients included in the registry were treated for atrial fibrillation, and 34% of all patients had been treated for fewer than 6 months.

Among the patients, 42% were older than 80 yr, and 69% of the patients had moderate to severe renal dysfunction. There were 26% of the patients who were also receiving other medications with antithrombotic properties such as nonsteroidal antiinflammatory drugs, aspirin, VKA, or heparin, concomitantly or within days before admission for bleeding. In 64% of the cases, patients were also treated with medications interacting with P-glycoprotein or CYP450.

The sites, types, and severity of bleeding events are summarized in table 2. Severe bleeding events were mainly major according to ISTH criteria<sup>19</sup> (74%) and spontaneous (79%).

In 94% of the cases, conventional routine hemostasis lab tests were performed. In 62% of the cases, a plasma concentration of dabigatran, rivaroxaban, or apixaban was determined on admission (table 3). The median concentrations of dabigatran, rivaroxaban, and apixaban were 162, 124, and 111 ng/ml, respectively. Among these patients, 9.2% had a plasma concentration that was lower than 50 ng/ml at the time of blood sampling. On the other hand, 6.6% of these patients had a DOAC concentration higher than 400 ng/ml, up to 3,500, 1,245, and 537 ng/ml for dabigatran, rivaroxaban, and apixaban, respectively. The median time between the last intake of DOACs and blood sampling was 12 h. In patients with a plasma concentration of less than 50 ng/ml, intracranial hemorrhage was observed in 42%, gastrointestinal bleeding was observed in 27%, and bleeding at other

sites was observed in 31% of the cases. Plasma concentrations were not significantly higher in patients treated with medications interacting with P-glycoprotein or CYP450, compared to patients who were not (table 4).

Bleeding management is described in table 4. PCCs (activated or nonactivated) were more frequently administered when bleeding occurred in a critical organ (intracranial or spinal; 57%) than in other sites (28%). PCCs were used in 28% of the patients for whom DOAC plasma concentrations were not determined. PCCs were used in 39% of cases where plasma concentrations were less than 50 ng/ml, 44% with plasma concentrations between 50 and 400 ng/ml, and 50% with plasma concentrations higher than 400 ng/ml ( $P = 0.001$ ). This study was not designed to address the hemostatic efficacy of PCC in specific bleeding sites. The adequacy of hemostasis provided by the PCC treatment was therefore assessed subjectively by local investigators with an ordinal scale: totally, partially, or not at all in 44, 37, and 19% of the cases, respectively.

Thirty days after bleeding, MACCEs occurred in 7.4% of the cases. On day 30, case fatality was 13.5% (95% CI, 11.0 to 16.2) with central nervous system causes in 42% of the cases (table 5).

Patients with gastrointestinal bleeding events were elderly (mean age,  $78.6 \pm 10$ ). Of these patients, 76% had a CHA2DS2Vasc score higher than 2, 24% had a history of heart failure, 25% had a history of stroke, and 20% had previous bleeding. The mortality in patients presenting with gastrointestinal bleeding was high (11.9% 30-day mortality).

### Discussion

Patients with bleeding during dabigatran, rivaroxaban, or apixaban treatment have been analyzed in several substudies of pivotal trials evaluating the efficacy and safety of dabigatran, rivaroxaban, and apixaban.<sup>4,6,20–23</sup> These studies aimed to compare the management and prognosis of major bleeding in patients treated with dabigatran or rivaroxaban *versus* warfarin. However, bleeding management during these treatments was not formally analyzed. Our registry aimed to describe the actual management of patients regarding the use of PCC and plasma concentration determination in a real world cohort and association with the outcome. This registry was not designed to obtain an estimation of incidence or the relative importance of bleeding in patients treated with dabigatran, rivaroxaban, or apixaban.

As observed in patients with bleeding events in phase III trials, the patients included in our registry were mainly elderly. Creatinine clearance was lower than 60 ml/min in 61% of the patients. Similar results have been previously reported.<sup>13,14</sup> Indeed, renal function may have been altered in different ways: (1) slow deterioration of renal function before the bleeding events due to comorbidities, treatment, or an acute illness (infection or dehydration) owing to accumulation of DOACs; (2) acute renal failure

**Table 1.** Demographic and Clinical Characteristics

	Dabigatran	Rivaroxaban	Apixaban	All
n	207	472	53	732
Age, yr, median [25th–75th]	81 [75–86]	77 [69–83]	78 [70–83]	78 [70–84]
Sex, % female	86 (42)	195 (41)	24 (45)	305 (42)
BMI	25 [23–28]	26 [24–29]	25 [23–28]	26 [23–29]
History (%)				
Hypertension	132 (65)	311 (67)	34 (65)	477 (65)
Heart failure or reduced LVEF	39 (19)	84 (18)	10 (19)	133 (18)
Coronary artery disease	44 (22)	91 (20)	13 (25)	148 (21)
Stroke	51 (25)	101 (22)	11 (21)	163 (23)
Diabetes mellitus	39 (19)	100 (22)	13 (25)	152 (21)
Peripheral vascular disease	52 (26)	100 (22)	13 (25)	165 (23)
Liver disease	9 (4.5)	14 (3.0)	2 (3.5)	25 (3.5)
Alcohol abuse	23 (11)	28 (6.0)	1 (1.9)	52 (7.2)
Bleeding	31 (15)	60 (13)	10 (19)	101 (14)
Creatinine clearance (Cockcroft and Gault), ml/min (%)				
> 60	41 (20)	148 (31)	12 (23)	201 (27)
30–59	102 (49)	214 (45)	25 (47)	341 (47)
15–29	38 (18)	43 (9.1)	10 (19)	91 (12)
< 15	9 (4.3)	6 (1.3)	2 (3.8)	17 (2.3)
Patients with AF				
n (%)	197 (95)	376 (80)	51 (96)	624 (85)
CHA2DS2-VASC score, median [25th–75th]	4 [3–4]	3 [3–4]	3 [3–4]	3 [3–4]
CHA2DS2-VASC > 2 (%)	156 (79)	292 (78)	40 (78)	488 (78)
Treatment regimen (%)				
150mg BID: 39 (20)		20mg OD: 187 (50)	2.5mg BID: 23 (45)	—
110mg BID: 146 (74)		15mg OD: 163 (43)	5mg BID: 27 (53)	—
75mg BID: 6 (3.0)		10mg OD: 12 (3.2)	—	—
Other and unknown: 6 (3.0)		Other and unknown: 14 (3.7)	Other and unknown: 1 (2.0)	—
Time between first treatment and bleeding (%)				
< 1 week	5 (2.5)	12 (3.2)	4 (7.8)	21 (3.4)
1 week to 1 month	11 (5.6)	37 (9.8)	12 (23)	60 (9.6)
1 month to 6 months	31 (15)	65 (17)	17 (33)	113 (18)
> 6 months	92 (47)	150 (40)	9 (18)	251 (40)
Unknown	58 (29)	112 (30)	9 (18)	179 (29)
Patients with VTE, n (%)	1 (0.5)	73 (16)	1 (1.9)	75 (10)
Treatment regimen (%)				
150mg OD: 1 (100)		15mg BID: 10 (14)	Unknown: 1 (100)	—
—		20mg OD: 52 (71)	—	—
—		15mg OD: 7 (9.6)	—	—
—		Other and unknown: 4 (5.5)	—	—
Time between first treatment and bleeding (%)				
< 1 week	—	5 (17)	—	5 (6.7)
1 week to 1 month	1 (100)	14 (19)	1 (100)	16 (21)
1 month to 6 months	—	32 (44)	—	32 (43)
> 6 months	—	20 (27)	—	20 (27)
Unknown	—	2 (2.4)	—	2 (2.7)
Indication unknown (%)	6 (2.9)	9 (1.9)	1 (1.9)	16 (2.2)
Off-label indication (%)	3 (1.4)	14 (3.0)	—	17 (2.3)
Medication taken within 3 days of admission				
n (%)	48 (23)	104 (22)	14 (26)	166 (23)
NSAIDs	6 (2.9)	10 (2.1)	—	16 (2.9)
Aspirin	28 (14)	72 (15)	11 (21)	111 (15)
Clopidogrel	6 (2.9)	14 (3.0)	1 (1.9)	21 (2.9)
VKA	3 (1.4)	2 (0.4)	1 (1.9)	6 (0.8)
LMWH	2 (1.0)	3 (0.6)	2 (3.8)	7 (0.9)
UFH	1 (0.5)	6 (0.3)	—	7 (0.9)
Medication interacting with PgP or CYP450 (n = 730) (%)	139 (67)	291 (62)	39 (74)	469 (64)

AF = atrial fibrillation; BID = twice a day; BMI = body mass index; CYP450 = cytochrome P450; LMWH = low molecular weight heparin; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal antiinflammatory drugs; OD = once a day; PgP = P-glycoprotein; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism; UFH = unfractionated heparin.



**Table 2.** Site Type and Severity of Bleeding

	Dabigatran (n = 207)	Rivaroxaban (n = 472)	Apixaban (n = 53)	All (n = 732)
Spontaneous bleeding, n (%)	156 (75)	384 (81)	40 (76)	580 (79)
Site n (%)				
Gastrointestinal	82 (52)	114 (30)	17 (43)	212 (37)
Intracranial	25 (16)	104 (27)	12 (30)	141 (24)
Intramuscular/skin	10 (6.4)	48 (13)	1 (2.5)	59 (10)
Epistaxis	9 (5.8)	42 (11)	2 (5.0)	53 (9.1)
Hematuria	16 (10)	22 (5.7)	2 (5.0)	40 (6.9)
Hemoptysis	4 (2.6)	16 (4.2)	3 (7.5)	23 (4.0)
Retroperitoneal	3 (1.9)	6 (1.6)	2 (5.0)	11 (1.9)
Pericardial	2 (1.3)	8 (2.1)	—	10 (1.7)
Intraperitoneal	2 (1.1)	7 (1.8)	—	9 (1.6)
Vaginal	—	5 (1.3)	1 (2.5)	6 (1.0)
Hemothorax	2 (1.3)	4 (1.3)	—	6 (1.0)
Intraarticular	1 (0.6)	3 (0.8)	—	4 (0.7)
Intraspinal	—	3 (0.8)	—	3 (0.5)
Other	1 (0.6)	2 (0.5)	—	3 (1.9)
Bleeding related to trauma (%)	51 (25)	86 (18)	13 (25)	150 (21)
Multiple trauma (%)	18 (35)	22 (26)	2 (15)	42 (28)
Head trauma (%)	33 (65)	59 (69)	10 (77)	102 (69)
Unknown (%)	—	5 (5.8)	1 (7.7)	5 (3.4)
Other (%)	—	2 (0.4)	—	2 (0.3)
Major bleeding (according to ISTH criteria) (%)	157 (76)	342 (73)	39 (74)	538 (74)

ISTH = International Society of Thrombosis and Hemostasis.

**Table 3.** Laboratory Results on Admission

	Dabigatran (n = 207)	Rivaroxaban (n = 472)	Apixaban (n = 53)	All (n = 732)
Hemoglobin				
n (%)	204 (99)	467 (99)	53 (100)	724 (99)
Median [25th–75th] (g/dl)	11.7 [8.6–13.3]	12.3 [9.6–13.8]	12.2 [10–14]	12.1 [9.3–13.7]
Platelet count				
n (%)	198 (96)	451 (96)	53 (100)	702 (96)
Median [25th–75th], g/l	204 [178–275]	226 [180–286]	214 [167–287]	225 [179–284]
Fibrinogen				
n (%)	147 (72)	294 (62)	18 (34)	479 (65)
Median [25th–75th], g/l	3.7 [3–4.3]	3.8 [3.1–4.5]	3.9 [3.3–4.5]	3.8 [3.1–4.4]
aPTT ratio				
n (%)	193 (93)	440 (93)	45 (85)	678 (93)
Median [25th–75th]	1.7 [1.4–2.2]	1.2 [1.0–1.3]	1.1 [1.1–1.3]	1.2 [1.1–1.5]
Prothrombin ratio				
n (%)	159 (77)	371 (79)	39 (74)	569 (78)
Median [25th–75th]	1.4 [1.2–1.7]	1.4 [1.2–1.7]	1.2 [1.1–1.3]	1.4 [1.2–1.7]
Plasma concentration of DOACs				
n (%)	123 (59)	285 (60)	34 (64)	452 (62)
Median (range), ng/ml	162 (3–3,500)	124 (0–1,245)	111 (18–537)	128 (0–3,500)
In patients with drugs interacting with PgP and/or CYP450				
n (%)	82 (40)	183 (39)	25 (47)	290 (40)
Median (range), ng/ml	165 (8–3,474)	120 (0–1,245)	109 (18–334)	125 (0–3,474)
Time between last intake and plasma concentration sampling				
n (%)	76 (37)	186 (39)	19 (36)	281 (38)
Median (range), h	8.5 (0.8–29)	14 (0.2–62)	11 (2.6–87)	12 (0.2–87)

aPTT = activated partial thromboplastin time; CYP450 = cytochrome P450; DOAC = direct oral anticoagulant; PgP = P-glycoprotein.

**Table 4.** Bleeding Management

	Dabigatran (n = 207)	Rivaroxaban (n = 472)	Apixaban (n = 53)	All (n = 732)
Transfusion, n (%)	94 (45)	150 (32)	17 (32)	261 (36)
Packed erythrocyte, n (%)	86 (42)	143 (30)	14 (26)	243 (33)
Platelets, n (%)	12 (5.8)	16 (3.4)	4 (7.5)	32 (4.4)
Fresh frozen plasma, n (%)	32 (16)	32 (6.8)	6 (11)	70 (9.6)
Fibrinogen concentrate, n (%)	5 (2.4)	6 (1.3)	—	11 (1.5)
PCC, n (%)	60 (29)	129 (27)	19 (36)	208 (28)
Total dose				
Median [25th–75th], U	3,000 [1,700–4,000]	3,000 [2,000–4,000]	3,000 [2,000–3,500]	3,000 [2,000–4,000]
Median [25th–75th], U/kg	40 [24–50]	44 [25–50]	42 [29–49]	43 [25–50]
Second dose, n (%)	5 (8.3)	20 (16)	2 (11)	27 (13)
aPCC, n (%)	26 (13)	41 (8.7)	6 (11)	73 (10)
Total dose				
Median [25th–75th], U	3,500 [2,500–4,000]	3,000 [2,500–3,575]	3,500 [3,000–4,000]	3,000 [2,500–4,000]
Median [25th–75th], U/kg	46 [40–52]	44 [37–50]	48 [46–48]	46 [38–50]
Second dose, n (%)	2 (7.7)	3 (7.3)	—	5 (6.8)
Recombinant factor VIIa	—	—	—	—
Tranexamic acid (%)	13 (6.3)	18 (3.8)	3 (5.8)	34 (4.7)
Hemodialysis (%)	7 (3.4)	2 (0.4)	—	9 (1.2)
Mechanical means (%)*	60 (29)	151 (32)	13 (25)	224 (31)
Intervention for hemostasis control (%)	48 (23)	119 (25)	8 (15)	175 (24)
Endoscopy (%)	26 (13)	64 (14)	7 (13)	97 (13)
Surgery (%)	4 (1.9)	17 (3.6)	1 (1.9)	22 (3)
Embolization (%)	18 (8.7)	38 (8.1)	—	56 (7.7)

\*Compression, gauze packing.

aPCC = activated PCC; PCC = prothrombin complex concentrate.

**Table 5.** 30-day Outcome

	Dabigatran (n = 207)	Rivaroxaban (n = 472)	Apixaban (n = 53)	All (n = 732)
MACCE, n (%)	21 (10)	30 (6.4)	3 (5.7)	54 (7.4)
Venous thromboembolism, n (%)	1 (0.5)	6 (1.3)	—	7 (1.0)
Ischemic stroke, n (%)	2 (1.0)	7 (1.5)	1 (1.9)	10 (1.4)
Systemic emboli, n (%)	—	2 (0.4)	—	2 (0.3)
Acute coronary syndrome, n (%)	5 (2.4)	4 (0.8)	1 (1.9)	10 (1.4)
Pulmonary edema, n (%)	8 (3.9)	10 (2.1)	—	18 (2.5)
Cardiogenic shock, n (%)	5 (2.4)	6 (1.3)	1 (1.9)	12 (1.6)
All causes of mortality, n	41	53	5	99
% [95% CI]	20 [15–26]	11 [7.6–15]	10 [3.3–21]	14 [11–16]
Mortality among patients with the following, % [95% CI]				
Intracranial hemorrhage (spontaneous)	36 [18–58]	28 [20–38]	17 [2.1–48]	28 [21–37]
Head trauma	24 [11–42]	14 [6–25]	10 [0.2–45]	17 [10–25]
Gastrointestinal bleeding	16 [8.8–27]	10 [5.1–17]	5.9 [0.1–29]	12 [7.8–17]
Cause of death (%)				
Neurologic/CNS	14 (6.8)	26 (5.5)	2 (3.8)	42 (5.7)
Bleeding	9 (4.3)	14 (3.0)	1 (1.9)	24 (3.3)
Cardiac	6 (2.9)	5 (1.1)	2 (3.8)	13 (1.8)
Sepsis	3 (1.4)	—	—	3 (0.4)
Other or undetermined	9 (4.3)	8 (1.7)	—	17 (2.3)

CNS = central nervous system; MACCE = major cerebral and cardiovascular events.

associated with the bleeding event; or (3) off-label use of DOACs (not recommended when creatinine clearance is lower than 15 ml/mn for rivaroxaban, apixaban, or edoxaban and lower than 30 ml/mn for dabigatran). Monitoring

renal function is recommended, at least yearly, to detect changes in renal function and adapt treatment doses, particularly in patients with previously altered renal function and elderly or frail patients.<sup>12</sup>

A major consideration of DOACs is that no specific reversal strategy was proposed before the manufacturers made them available for clinical use. Antidotes were developed several years after the first approval of DOACs.<sup>24</sup> To date, except for dabigatran, reversal strategies rely on nonspecific measures and on the administration of hemostatic agents, mainly activated or nonactivated PCC.<sup>12</sup> Idarucizumab, a humanized monoclonal antibody that selectively binds dabigatran, has been recently approved.<sup>13</sup> Andexanet alfa is a recombinant modified human factor Xa decoy protein that has been shown to reverse the inhibition of factor Xa in healthy volunteers<sup>25</sup> and patients.<sup>14</sup> Ciraparantag (PER977) is a small cationic and water-soluble molecule designed to bind with high affinity to oral FXa inhibitors (edoxaban, rivaroxaban, and apixaban) and to dabigatran.<sup>26</sup>

Little information has been made available on the use and timing of specific reversal strategies in pivotal studies on DOACs.<sup>4,6,23</sup> In these studies, few patients with major bleeding have been treated with PCCs. In the Dresden registry, among 1,082 bleeding events observed during rivaroxaban exposure, 59% were classified as ISTH minor bleeding, 35% were classified as ISTH nonmajor clinically relevant bleeding, and 66 (6.1%) patients had major bleeding treated with PCC in 9.1% of the cases.<sup>27</sup> Our registry includes a population principally with major bleeding events that is large enough to obtain a reasonable estimate for specific management strategies and outcome.

The use of PCCs to reverse the anticoagulation action of DOACs has not yet been assessed in clinical practice but is still suggested in international and national guidelines.<sup>11,12</sup> Only animal<sup>18,28</sup> or healthy volunteer studies<sup>7,9,29</sup> have assessed the efficacy of PCCs (activated or not) on different endpoints. A study of healthy volunteers compared the effect of a three-factor with a four-factor PCC on reversal of the anticoagulant effects of rivaroxaban.<sup>30</sup> Both four-factor PCCs and three-factor PCCs partially reversed the anticoagulant effects of rivaroxaban with good tolerance and no signs of thromboembolic events. In our registry, only four-factor PCCs or FEIBA were used. The present study shows that 38.4% of the patients were treated with PCCs with a distribution between activated or nonactivated PCC that is similar in patients treated with each DOAC. The use of PCC was related to the anatomic site of the bleeding. A majority of investigators consider that the use of PCCs partially or totally contributed to cessation of bleeding.

The use of coagulation testing during the clinical development of DOACs was not used in clinical trials based on considerations they would not require monitoring because of their highly predictable pharmacokinetics and therapeutic effects. Although this position has been challenged in subsequent publications regarding dabigatran,<sup>31</sup> specific plasma concentration techniques have been developed<sup>32</sup> for each DOAC, in theory either to answer specific questions (*i.e.*, compliance to treatment) or to guide periprocedural or bleeding management.<sup>11</sup> Indeed, numerous case reports and

series have shown that bleeding events could be related to the high plasma concentrations of these new agents,<sup>31,33</sup> as already observed with other anticoagulant agents.

In the present study, the plasma concentration of DOACs was determined on admission in 62% of the patients. Among these patients, 9.2% had a plasma concentration that was lower than 50 ng/ml at the time of blood sampling. These results could in part be explained by the time between the last dose and sampling. On the other hand, 6.6% of these patients had a DOAC concentration higher than 400 ng/ml, suggesting that in several patients, DOACs could accumulate owing to renal failure or major drug interaction. Very high DOAC plasma concentrations (higher than 400 ng/ml) have been observed in previous studies, either in cases of intentional overdose cohorts<sup>34</sup> and particularly in the context of bleeding.<sup>13,14</sup>

In our registry, 63% of the patients were also treated with medication interacting with the pharmacokinetics of DOACs. However, DOAC plasma concentration was not significantly higher than in patients not treated with these medications. The importance of these potential interactions in explaining high DOAC plasma concentration was not explored in the present study.

In addition to these observations, the usefulness of DOAC plasma concentration determination to guide major bleeding management has never been evaluated. The present study shows that plasma concentration was positively related to the use of PCCs. Hence, plasma concentration could be of major importance in identifying patients in whom the use of an antidote or, if not available, PCC could be useful in reversing the anticoagulant effects of DOACs. However, our study does not show that this strategy lowers mortality.

Several analyses of mortality related to major bleeds have been performed from pivotal studies of DOACs. Thirty-day mortality after the first major bleed in phase III trials comparing dabigatran with warfarin was 9.1% in the dabigatran group and 13.0% in the warfarin group.<sup>23</sup> Using data from the ROCKET AF study, the outcomes after major bleeding, including all causes of death, were similar in patients treated with rivaroxaban and warfarin (20.4 *vs.* 25.6% in the rivaroxaban and warfarin group, respectively).<sup>4</sup> In the ARISTOTLE study, 8.9% with major nonintracranial bleeding died in the apixaban arm, and 9.5% died in the warfarin arm. Of those with intracranial hemorrhage, 45.3% died in the apixaban arm, and 42.3% died in the warfarin arm.<sup>6</sup>

The outcomes of intracranial hemorrhage in the ROCKET AF and RE-LY studies have been analyzed more specifically.<sup>21,22</sup> In the RE-LY study, 154 intracranial hemorrhages occurred in 153 subjects.<sup>22</sup> The mortality rate ranged from 24 to 49% depending on the intracranial location of the bleeding in both the dabigatran and the warfarin groups. During ROCKET AF follow-up, 172 patients experienced 174 intracranial bleeding episodes.<sup>21</sup> Mortality ranged from 20 to 69% depending on the intracranial location of the bleeding in both the rivaroxaban and the warfarin groups.<sup>4</sup>

In the present study, the mortality for spontaneous intracranial hemorrhage ( $n = 141$ ) was 36, 28, and 17% in patients treated with dabigatran, rivaroxaban, and apixaban, respectively, with large confidence intervals.

Several factors impair the comparability with different studies on bleeding complications: history, severity, cause, and sites of bleeding. Depending on the cause of bleeding, mortality can differ greatly owing to the rate of intracranial hemorrhage, whose mortality rate is high,<sup>35</sup> and to other anatomic sites with lower mortality.

Our study has several strengths. The majority of the bleeding events described are classified based on major ISTH criteria. A detailed clinical and biologic assessment was available for most of the patients in this real world cohort. This included the plasma concentrations of dabigatran, rivaroxaban, or apixaban in a large subset of patients. Step-by-step management of these bleeding episodes is described including the use of hemostatic agents as suggested in most guidelines.

Our study has the limitations inherent to the observational nature of the study. This impacts the distribution of the bleeding sites and the severity of the cases. Moreover, the rate of inclusion among the 36 participating centers ranged from 1 to 67 depending on the investigator's department.

## Conclusions

The data available in the GIHP-NACO registry provide an instant picture of the complex management of DOAC-induced major bleeding events in two European countries. Despite compliance to specific management, including the use of hemostatic agents or plasma concentration determination, mortality remains high. Specific analysis of bleeding sites is needed to assess the role of present or future (antidote) reversal strategies to improve the outcome of major bleeding in patients treated with DOACs.

## Research Support

This study was supported by an unrestricted grant from Octapharma (Boulogne-Billancourt, France), CSL-Behring (Marburg, Germany), and LFB (Les Ulis, France).

## Competing Interests

Dr. Albaladejo and Dr. Samama report personal fees and nonfinancial support from Bayer (Lyon, France), Boehringer Ingelheim (Paris, France), Daiichi Sankyo (Rueil-Malmaison, France), Bristol-Myers Squibb (Rueil-Malmaison, France), and Pfizer (Paris, France) outside the submitted work; Dr. Gruel reports personal fees from Boehringer Ingelheim (Paris, France) and Bristol-Myers Squibb (Rueil-Malmaison, France) and personal fees and nonfinancial support from Bayer (Lyon, France) outside the submitted work. The other authors declare no competing interests.

## Correspondence

Address correspondence to Dr. Albaladejo: Department of Anesthesiology and Intensive Care Medicine, Grenoble-Alpes University Hospital, 38043 Grenoble, France. [PALbaladejo@](mailto:PALbaladejo@chu-grenoble.fr)

[chu-grenoble.fr](http://chu-grenoble.fr). Information on purchasing reprints may be found at [www.anesthesiology.org](http://www.anesthesiology.org) or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

## References

1. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV: Effectiveness and safety of novel oral anti-coagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: A systematic review and meta-analysis. *J Thromb Haemost* 2014; 12:320–8
2. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM: Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet* 2014; 383:955–62
3. Larsen TB, Skjøth F, Nielsen PB, Kjeldgaard JN, Lip GY: Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. *BMJ* 2016; 353:i3189
4. Piccini JP, Garg J, Patel MR, Lokhnygina Y, Goodman SG, Becker RC, Berkowitz SD, Breithardt G, Hacke W, Halperin JL, Hankey GJ, Nessel CC, Mahaffey KW, Singer DE, Califf RM, Fox KA; ROCKET AF Investigators: Management of major bleeding events in patients treated with rivaroxaban vs. warfarin: Results from the ROCKET AF trial. *Eur Heart J* 2014; 35:1873–80
5. Majeed A, Meijer K, Larrazabal R, Arnberg F, Luijckx GJ, Roberts RS, Schulman S: Mortality in vitamin K antagonist-related intracerebral bleeding treated with plasma or 4-factor prothrombin complex concentrate. *Thromb Haemost* 2014; 111:233–9
6. Held C, Hylek EM, Alexander JH, Hanna M, Lopes RD, Wojdyla DM, Thomas L, Al-Khalidi H, Alings M, Xavier D, Ansell J, Goto S, Ruzyllo W, Rosenqvist M, Verheugt FW, Zhu J, Granger CB, Wallentin L: Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: Insights from the ARISTOTLE trial. *Eur Heart J* 2015; 36:1264–72
7. Zahir H, Brown KS, Vandell AG, Desai M, Maa JF, Dishy V, Lomeli B, Feussner A, Feng W, He L, Grosso MA, Lanz HJ, Antman EM: Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. *Circulation* 2015; 131:82–90
8. Martin AC, Le Bonniec B, Fischer AM, Marchand-Leroux C, Gaussem P, Samama CM, Godier A: Evaluation of recombinant activated factor VII, prothrombin complex concentrate, and fibrinogen concentrate to reverse apixaban in a rabbit model of bleeding and thrombosis. *Int J Cardiol* 2013; 168:4228–33
9. Marlu R, Hodaj E, Paris A, Albaladejo P, Cracowski JL, Cracowski JL, Pernod G: Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover *ex vivo* study in healthy volunteers. *Thromb Haemost* 2012; 108:217–24
10. Lee FM, Chan AK, Lau KK, Chan HH: Reversal of new, factor-specific oral anticoagulants by rFVIIa, prothrombin complex concentrate and activated prothrombin complex concentrate: A review of animal and human studies. *Thromb Res* 2014; 133:705–13
11. Pernod G, Albaladejo P, Godier A, Samama CM, Susen S, Gruel Y, Blais N, Fontana P, Cohen A, Llau JV, Rosencher N, Schved JF, de Maistre E, Samama MM, Mismetti P, Sié P; Working Group on Perioperative Haemostasis: Management of major bleeding complications and emergency surgery



- in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: Proposals of the working group on perioperative haemostasis (GIHP) - March 2013. *Arch Cardiovasc Dis* 2013; 106:382–93
12. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P: Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015; 17:1467–507
  13. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI: Idarucizumab for dabigatran reversal. *N Engl J Med* 2015; 373:511–20
  14. Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, Bronson MD, Lu G, Conley PB, Verhamme P, Schmidt J, Middeldorp S, Cohen AT, Beyer-Westendorf J, Albaladejo P, Lopez-Sendon J, Goodman S, Leeds J, Wiens BL, Siegal DM, Zotova E, Meeks B, Nakamya J, Lim WT, Crowther M; ANNEXA-4 Investigators: Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016; 375:1131–41
  15. Ghadimi K, Levy JH, Welsby IJ: Prothrombin complex concentrates for bleeding in the perioperative setting. *Anesth Analg* 2016; 122:1287–300
  16. Dickneite G, Hoffman M: Reversing the new oral anticoagulants with prothrombin complex concentrates (PCCs): What is the evidence? *Thromb Haemost* 2014; 111:189–98
  17. Schulman S and Kearon C: Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3:692–4
  18. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S; Subcommittee on Control of Anticoagulation: Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: Communication from the SSC of the ISTH. *J Thromb Haemost* 2015; 13:2119–26
  19. Schulman S, Carrier M, Lee AY, Shivakumar S, Blostein M, Spencer FA, Solymoss S, Barty R, Wang G, Heddl N, Douketis JD; Periop Dabigatran Study Group: Perioperative management of dabigatran: A prospective cohort study. *Circulation* 2015; 132:167–73
  20. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, Huber K, Jansky P, Steg PG, Hanna M, Thomas L, Wallentin L, Granger CB: Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, characteristics, and clinical outcomes. *J Am Coll Cardiol* 2014; 63:2141–7
  21. Hankey GJ, Stevens SR, Piccini JP, Lokhnygina Y, Mahaffey KW, Halperin JL, Patel MR, Breithardt G, Singer DE, Becker RC, Berkowitz SD, Paolini JF, Nessel CC, Hacke W, Fox KA, Califf RM; ROCKET AF Steering Committee and Investigators: Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: The rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. *Stroke* 2014; 45:1304–12
  22. Hart RG, Diener HC, Yang S, Connolly SJ, Wallentin L, Reilly PA, Ezekowitz MD, Yusuf S: Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: The RE-LY trial. *Stroke* 2012; 43:1511–7
  23. Majeed A, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, Brueckmann M, Fraessdorf M, Yusuf S, Schulman S: Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation* 2013; 128:2325–32
  24. Greinacher A, Thiele T, Selleng K: Reversal of anticoagulants: An overview of current developments. *Thromb Haemost* 2015; 113:931–42
  25. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, Mar FA, Gold A, Crowther MA: Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* 2015; 373:2413–24
  26. Ansell JE, Bakhru SH, Laila BE, Steiner SS, Grosso M, Brown K, Dishy V, Noveck RJ, Costin JC: Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* 2014; 371:2141–2
  27. Beyer-Westendorf J, Förster K, Pannach S, Ebertz F, Gelbricht V, Thieme C, Michalski F, Köhler C, Werth S, Sahin K, Tittel L, Hänsel U, Weiss N: Rates, management, and outcome of rivaroxaban bleeding in daily care: Results from the Dresden NOAC registry. *Blood* 2014; 124:955–62
  28. Honickel M, Treutler S, van Ryn J, Tillmann S, Rossaint R, Grotke O: Reversal of dabigatran anticoagulation *ex vivo*: Porcine study comparing prothrombin complex concentrates and idarucizumab. *Thromb Haemost* 2015; 113:728–40
  29. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M: Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in healthy subjects. *Circulation* 2011; 124:1573–9
  30. Levi M, Moore KT, Castillejos CF, Kubitz D, Berkowitz SD, Goldhaber SZ, Raghoobar M, Patel MR, Weitz JI, Levy JH: Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost* 2014; 12:1428–36
  31. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L; RE-LY Investigators: The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol* 2014; 63:321–8
  32. Samama MM, Contant G, Spiro TE, Perzborn E, Guinet C, Gourmelin Y, Le Flem L, Rohde G, Martinoli JL: Rivaroxaban Anti-Factor Xa Chromogenic Assay Field Trial Laboratories: Evaluation of the anti-factor Xa chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. *Thromb Haemost* 2012; 107:379–87
  33. Warkentin TE, Margetts P, Connolly SJ, Lamy A, Ricci C, Eikelboom JW: Recombinant factor VIIa (rFVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood* 2012; 119:2172–4
  34. Cuker A, Siegal DM, Crowther MA, Garcia DA: Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol* 2014; 64:1128–39
  35. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, Flechsenhar J, Neugebauer H, Jüttler E, Grau A, Palm F, Röther J, Michels P, Hamann GF, Hüwel J, Hagemann G, Barber B, Terborg C, Trostorf F, Bärner H, Roth A, Wöhrle J, Keller M, Schwarz M, Reimann G, Volkmann J, Müllges W, Kraft P, Classen J, Hobohm C, Horn M, Milewski A, Reichmann H, Schneider H, Schimmel E, Fink GR, Dohmen C, Stetefeld H, Witte O, Günther A, Neumann-Haefelin T, Racs AE, Nueckel M, Erbguth F, Kloska SP, Dörfler A, Köhrmann M, Schwab S, Huttner HB: Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA* 2015; 313:824–36

## Appendix: GIHP-NACO Study Group: Severe Bleedings

Sophie Kauffmann, M.D., Jean Etienne Bazin, M.D., Ph.D., Nicolas Combaret, M.D., Anne Laure Cherprenet, M.D., Moustafa Fares, M.D., Sophie Dufraisie, M.D., Clermont-Ferrand University Hospital, Clermont-Ferrand, France (n = 67); Pierre Sié, M.D., Ph.D., Vincent Minville, M.D., Ph.D., Vincent Mémier, M.D., Toulouse University Hospital, Toulouse, France (n = 66); Pierre Morange, M.D., Ph.D., Marc Leone, M.D., Ph.D., William Cohen, M.D., Nadège Néant, M.D., Pierre Suchon, M.D., Assistance Publique- Hôpitaux de Marseille, Marseille, France (n = 64); Pierre Albaladejo, M.D., Ph.D., Gilles Pernod, M.D., Ph.D., Raphaël Marlu, M.D., Ph.D., Françoise Carpentier, M.D., Ph.D., Pascal Defaye, M.D., Ph.D., Grenoble University Hospital, Grenoble, France (n = 56); Patrick Mismetti, M.D., Ph.D., Alain Viallon, M.D., Ph.D., Serge Molliex, M.D., Ph.D., Julien Lanoiselée, M.D., Saint Etienne University Hospital, Saint Etienne, France (n = 55); Vincent Piriou, M.D., Ph.D., Jean Stéphane David, M.D., Ph.D., Carine Delaleu-Rague, M.D., Mathilde Lefèvre, M.D., Sophie Lagrange, M.D., Hospices Civils de Lyon, Lyon-Sud University Hospital, Pierre Benite, France (n = 48); Yves Gruel, M.D., Ph.D., Laurent Ardillon, M.D., Tours University Hospital, Tours, France (n = 46); Lorenn Bellamy, M.D., Yves Ozier, M.D., Ph.D., Brest University Hospital, Brest, France (n = 42); Emmanuel de Maistre, M.D., Ph.D., Julien Bovet, M.D., Dijon University Hospital, Dijon, France (n = 39); Annick Steib, M.D., Ph.D., Sonia Mebaouj, M.D., Louis Profumo, M.D., Strasbourg University Hospital, Strasbourg, France (n = 29); Stéphanie Roulet, M.D., Ph.D., Bordeaux University Hospital, Bordeaux, France (n = 27); David Smadja, M.D., Ph.D., Guy Meyer, M.D., Ph.D., Didier Journois, M.D., Ph.D., Assistance Publique-Hôpitaux de Paris, Georges Pompidou University Hospital, Paris, France (n = 23); Albert Trinh-Duc, M.D., Thibault Viard, M.D., Agen General Hospital, Agen, France (n = 21); Loic Belle, M.D., Ph.D., Albrice Levrat, M.D., Etienne Gautheron, M.D., Frédéric Heluwaert, M.D., Annecy Regional Hospital, Annecy, France (n = 19); Sylvie Schlumberger, M.D., Centre Médico-Chirurgical Foch, Suresnes, France (n = 18); Antonia Blanié, M.D., Dan Benhamou,

M.D., Ph.D., Assistance Publique-Hôpitaux de Paris, Bicêtre University Hospital, Le Kremlin Bicêtre, France (n = 17); Charles Marc Samama, M.D., Ph.D., Claire Flaujac, M.D., Nadia Rosencher, M.D., Assistance Publique-Hôpitaux de Paris, Cochin University Hospital, Paris, France (n = 13); Hélène Beloeil, M.D., Ph.D., Catherine Blery, M.D., Lauren Daviet, M.D., Pierre Gueret, M.D., Ph.D., Rennes University Hospital, Rennes, France (n = 11); David Faraoni, M.D., Ph.D., Brugmann University Hospital, Brussels, Belgium, (n = 10); Jean François Schved, M.D., Ph.D., Pauline Deras, M.D., Samir Jaber, M.D., Ph.D., Montpellier University Hospital, Montpellier, France (n = 10); Pierre Yves Gueugniaud, M.D., Ph.D., Bernard Floccard, M.D., Hospices Civils de Lyon, Edouard Herriot University Hospital, Lyon, France (n = 8); Karim Asehnoune, M.D., Ph.D., Jérôme Paulus, M.D., Omar Amrani, M.D., Nantes University Hospital, Nantes, France (n = 7); Marie Caroline Gonthier, M.D., Marie Geneviève Huisse, M.D., Assistance Publique-Hôpitaux de Paris, Bichat University Hospital, Paris, France (n = 6); Julien Josserand, M.D., Emmanuelle de Raucourt, M.D., Assistance Publique-Hôpitaux de Paris, Beaujon University Hospital, Clichy, France (n = 5); Cécile Defournel, M.D., Alpes Léman Hospital, Contamine sur Arve, France (n = 5); Yohann Dubois, M.D., Stéphane Bouvier, M.D., Groupe Hospitalier Mutualiste, Grenoble, France (n = 4); Pierre-Marie Roy, M.D., Ph.D., Sigismond Lasocki, M.D., Ph.D., Angers University Hospital, Angers, France (n = 4); Christian Carmagnac, M.D., Catherine Chastagner, M.D., Jean Marc Thouret, M.D., Chambéry General Hospital, Chambéry, France (n = 3); Marie Antoinette Sevestre, M.D., Ph.D., Amiens University Hospital, Amiens, France (n = 3); Eric Meaudre, M.D., Pierre-Julien Cungi, M.D., Saint Anne Military Hospital, Toulon, France (n = 2); Sophie Susen, M.D., Ph.D., Lille University Hospital, Lille, France (n = 1); Jean Yves Lefrant, M.D., Ph.D., Nimes University Hospital, Nimes, France (n = 1); Stéphane Macey, M.D., Gap General Hospital, Gap, France (n = 1); Jean Baptiste Rieu, M.D., Castres General Hospital, Castres, France (n = 1); Anne Godier, M.D., Ph.D., Rothschild Foundation, Paris, France (n = 1).