Received: 21 November 2019 | Revised: 4 February 2020 | Accepted: 25 February 2020

DOI: 10.1002/rth2.12336

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

Emergencies on direct oral anticoagulants: Management, outcomes, and laboratory effects of prothrombin complex concentrate

Roisin Bavalia MD[1] | Rahat Abdoellakhan PharmD[2] | Herm Jan M. Brinkman PhD[3] | Marjolein P. A. Brekelmans MD, PhD[1] | Eva N. Hamulyák MD[1] | Marleen Zuurveld[3] | Barbara A. Hutten PhD[4] | Peter E. Westerweel MD, PhD[5] | Renske H. Olie MD[6] | Hugo ten Cate MD, PhD[6] | Marieke Kruip MD, PhD[7] | Saskia Middeldorp MD, PhD[1] | Karina Meijer MD, PhD[2] | Michiel Coppens MD, PhD[1]

[1]Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[2]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

[3]Department of Molecular and Cellular Hemostasis, Sanquin Research, Amsterdam, The Netherlands

[4]Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[5]Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, The Netherlands

[6]Department of Internal Medicine, Maastricht University Medical Center+, Maastricht, The Netherlands

[7]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence
Roisin Bavalia, Department of Vascular Medicine, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
Email: r.bavalia@amsterdamumc.nl

Funding information
ZonMw, Grant/Award Number: 836021017

Handling Editor: Dr Cihan Ay

Abstract

Background: In the initial absence of specific reversal agents for factor Xa inhibitors (FXa-Is), prothrombin complex concentrate (PCC) as a hemostatic agent has been recommended by guidelines. Since 2017, idarucizumab has been registered for dabigatran reversal. Still, data on the clinical outcome of direct oral anticoagulant (DOAC)-related emergencies (major bleeding or urgent interventions) is scarce. In addition, it is unknown to what extent PCC restores thrombin generation in FXa-I–related emergencies. Our aim was to describe management and clinical outcomes of DOAC-related emergencies and to assess the laboratory effect of PCC in patients with FXa-I emergencies.

Methods: In this prospective cohort study in 5 Dutch hospitals, patients presenting with DOAC-related emergencies were eligible. The primary outcome was effective hemostasis according to the ISTH definition. Safety outcomes were 30-day mortality and thromboembolic rate. In patients treated with PCC, additional blood samples were taken to assess the effect on thrombin generation.

Results: We included 101 patients with major bleeding (FXa-I, 76; dabigatran, 25) and 21 patients requiring an urgent intervention (FXa-I, 16; dabigatran, 5). Of patients with major bleeding, 67% were treated with PCC or idarucizumab. Effective hemostasis, 30-day mortality, and thromboembolism rate were 67%, 22%, and 1%, respectively. In a subset of bleeding patients on FXa-I managed with PCC, thrombin generation increased, with 96% immediately after PCC administration. In patients requiring an urgent intervention, effective hemostasis, 30-day mortality, and thromboembolic rate were 95%, 14%, and 5%.

Conclusions: Effective hemostasis was achieved in the majority of patients presenting with DOAC-related emergencies;, thromboembolic complications were rare, and mortality was quite high.

KEYWORDS

dabigatran, emergencies, factor Xa inhibitors, hemorrhage, idarucizumab, prothrombin complex concentrates

Essentials

- In 121 direct oral anticoagulant–related emergencies, two thirds of patients achieved effective hemostasis.
- In those with life-threatening FXa inhibitor–related bleeding, effective hemostasis was 70% when PCC was used.
- This study demonstrates that PCC swiftly restores thrombin generation in bleeding patients on FXa inhibitors.
- The hemostatic efficacy achieved by PCC seems comparable to that achieved by andexanet alfa, and therefore a randomized comparison would be valuable.

1 | INTRODUCTION

Worldwide, millions of patients with atrial fibrillation (AF) and venous thromboembolism (VTE) as primary indications are treated with oral anticoagulant agents. While highly effective, the benefit of oral anticoagulation is partly offset by the risk of bleeding complications. The incidence of major bleeding while on oral anticoagulation is estimated at 2%-3% per year with a case fatality rate of 7.6% (95% confidence interval [CI], 6.5%-8.7%) for direct oral anticoagulants (DOACs) and 11% (95% CI, 9.2%-13.1%) for vitamin K antagonist (VKA)-related bleeding.[1-6]

Currently, the DOACs apixaban, dabigatran etexilate (dabigatran), edoxaban, and rivaroxaban are replacing VKAs in the majority of patients with AF and VTE.[7] Compared with VKAs, DOACs are at least as effective in preventing thromboembolic events, while the risk of major bleeding complications differs; in comparison with VKAs, DOACs reduce the risk of intracranial hemorrhage (ICH) and fatal bleeding by 50% and increase the risk of gastrointestinal bleeding by 25%.[1,8,9] Consequently, international guidelines recommend DOACs over VKAs for patients with AF and VTE.[10,11]Nevertheless, due to the vast numbers of patients on long-term oral anticoagulation, DOAC-related major bleeding is still encountered frequently, and optimal management of these patients is paramount to prevent permanent disabilities and death.

One aspect of the management of patients with a major bleeding is to restore functional hemostasis by rapidly reversing the effects of the anticoagulant. However, upon registration of the first DOAC in 2008, no specific reversal agent was available, which led to considerable concern on the safety of DOACs, especially for patients deemed to be at the highest risk of bleeding.[12] Idarucizumab, a high-affinity antibody specific for dabigatran, was approved for emergency reversal of dabigatran in patients with major bleeding or urgent interventions a few years later.[13] For the reversal of the direct factor Xa inhibitors (FXa-Is) apixaban and rivaroxaban for major bleeding, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have recently approved andexanet alfa.[14] Andexanet alfa is neither approved for reversal of the FXa-Is edoxaban and betrixaban, nor is it approved for reversal in nonbleeding patients requiring an urgent intervention. Prior to the regulatory approval of idarucizumab and andexanet alfa, international guidance documents recommended the use of 4-factor prothrombin complex concentrate (PCC) at a dose of 25-50 IU/kg for DOAC-related life-threatening situations.[15] These recommendations were largely based on crossover studies, demonstrating that PCC in a dose of 50 IU/kg swiftly restored endogenous thrombin potential (ETP) to pre-anticoagulant levels in healthy volunteers treated with FXa-Is.[16-19] Major bleeding itself, however, causes systemic coagulation activation to achieve hemostasis. Therefore, the overall effect of PCC might be different in bleeding versus nonbleeding patients. To our knowledge, no study has thus far evaluated the effects of PCC on coagulation parameters in patients that present with bleeding.

Studies evaluating the clinical management and outcome of patients presenting with a DOAC-related emergency are scarce. In a recently published meta-analysis of 10 single-arm case series consisting of 340 patients treated with PCC for FXa-I–related major bleeding, hemostasis was achieved in the majority of patients.[20] However, these studies were quite heterogeneous with respect to eligibility criteria, follow-up period, and definition of outcomes, including hemostasis. Only 2 studies evaluated effective hemostasis according to the ISTH definition.[21,22] These criteria for hemostatic efficacy were developed in conjunction with the FDA for the trial that led to regulatory approval of PCC for management of VKA-related emergencies in the United States.[23] According to these criteria, hemostasis can be classified as excellent, good, or poor, with different criteria for different sites of bleeding (musculoskeletal, intracranial, or other nonvisible bleeding), wherein effective hemostasis is defined as either excellent or good hemostasis. This scoring system has undergone minor modifications and is frequently used

in contemporary reversal studies evaluating the outcome of bleeding on anticoagulant therapy.[24] Even though there is an acknowledged definition for effective hemostasis, interpretation of data on efficacy of reversal agents remains a challenge due to the lack of placebo-controlled arms. Therefore, it is uncertain if hemostatic therapies over supportive management have additional benefit. As providing a placebo control group in this study subject is unethical and probably will never be conducted, we believe it is of great importance to provide more data on this topic from different countries and settings worldwide to gain more insight on the interpretation of the single-arm studies data.

The primary aim of this study was to describe the management and outcome of DOAC-related emergencies in terms of effective hemostasis according to the criteria of the ISTH and to evaluate effective hemostasis and risk of thromboembolic events in those patients who were treated with PCC. The secondary aim was to evaluate the effects of PCC on coagulation parameters in actively bleeding patients.

2 | METHODS

2.1 | Study design and population

We conducted a multicenter, prospective cohort study evaluating the clinical management of DOAC-related emergencies from December 2014 up until December 2018. Consecutive patients were enrolled in 5 Dutch hospitals (4 academic and 1 teaching hospital). The ethics committee of Amsterdam Medical Center approved the study protocol. Patients were eligible for participation if they were 18 years or older, received treatment with a DOAC (apixaban, dabigatran, edoxaban, rivaroxaban) for any indication, and presented with a DOAC-related emergency, that is, major bleeding or the need for an urgent intervention within the next 8 hours. Major bleeding was defined as any bleeding resulting in death; symptomatic bleeding in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, and pericardial bleeding and muscle bleeding resulting in compartment syndrome) or symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2 g/dL (1.2 mmol/L) or resulting in transfusion of at least 2 units of erythrocytes, following the ISTH criteria.[25] Eligibility was adjudicated by the local coordinators in every medical center and reevaluated by the national coordinator in the Amsterdam UMC. If in doubt, a third author (MC) was involved in assessing eligibility.

In patients who met the criteria for ISTH major bleeding, bleeding was further subclassified according to the severity of the clinical presentation and course, using a previously established scoring system, which is shown in Table 1.[26] Urgent interventions were defined as any nonbleeding emergency situations in which an intervention was indicated within 8 hours. We categorized the urgent interventions in situations leading to a procedure in the operating theater (surgery) and situations that did not (other procedures).

Patients participating in trials evaluating efficacy and safety of other investigational products were excluded. The treatment and management of the DOAC-related emergency was at the discretion of the treating physician, and therefore follow-up of the emergency was not protocolled. Any interventions to control bleeding and perioperative strategies were recorded but not part of the study protocol. We collected data of the included patients within 48 hours of presentation by reviewing the electronic patient chart and by a clinical or telephone visit for the patients who gave consent. In case of uncertainties, we obtained additional information from the treating physicians, the patient, patient's representatives, or the general practitioner.

Patients underwent additional blood draws at presentation (T0) and 4-8 hours after presentation (T2). In patients who received PCC for the FXa-I–related emergency, samples were drawn 15-30 minutes after administration of PCC (T1). In patients undergoing additional blood draws, we obtained written informed consent. Patients were followed until 30 days after inclusion or death.

TABLE 1 Established scoring system for major bleeding according to the severity of the clinical presentation

Category	Description
1	Bleeding events presenting without any clinical emergency
2	All bleeding events that could not be classified to any of the other 3 categories, as they presented with the need for some measures but without clear urgency
3	Bleeding events presenting with great medical emergency, eg, with hemodynamic instability, or cerebral major bleeding presenting with neurological symptoms
4	Bleeding events already fatal before or almost immediately upon entering the hospital

2.2 | Outcomes

2.2.1 | Hemostatic efficacy

The primary clinical outcome in patients presenting with a DOAC-related bleeding was effective hemostasis at 24 hours after presentation, according to the ISTH definition.[23,24] We assessed ICH by the ISTH definition and non-ICH by the original criteria by Sarode at 24 hours.[23,24] As effective hemostasis was evaluated up to 24 hours only, we considered rebleeding events after 24 hours until 30 days as a secondary efficacy outcome. For patients presenting with the need for an acute urgent intervention, we defined (surgical) hemostasis as effective when no major bleeding occurred within 7 days after the urgent intervention.[27] We defined poor hemostasis if a major bleeding occurred within 7 days after the urgent intervention. We chose this cutoff as we thought of 7 days being the most clinically relevant period. Hemostatic efficacy was assessed by the local coordinators in every center and reevaluated by the national coordinator in the Amsterdam UMC. If in doubt, a third author (MC) was involved in assessing hemostatic efficacy.

2.2.2 | Safety outcomes

Safety outcomes consisted of arterial (acute coronary syndrome, stroke, transient ischemic attack, or systemic embolism) and venous thromboembolism (pulmonary embolism, deep vein thrombosis) and mortality up to 30 days after presentation with the emergency.

2.3 | Laboratory assays

We determined FXa-I and dabigatran levels using Biophen direct factor Xa and Hemoclot direct thrombin inhibitor assay kits (Hyphen Biomed) with apixaban, dabigatran, edoxaban, and rivaroxaban calibrators and control plasma (Hyphen Biomed) where appropriate. We performed thrombin generation (calibrated automated thrombography [CAT] method) as per manufacturer's instruction (Thrombinoscope Stago) with some minor modifications. Final plasma concentration was 50% v/v (60 µL of plasma, 20 µL of buffered saline, 20 µL of calibrator or PPP reagent, 20 µL of FluCa). Calibrator and PPP reagent (5 PM tissue factor) were from Thrombinoscope. FluCa was a 3-mM mixture of the fluorogenic thrombin substrate z-Gly-Gly-Arg-AMC (Bachem) in 90 mM of $CaCl_2$. To eliminate calibrator inhibition during measurement, dabigatran-containing samples were treated with DOAC Stop (Haematex Research) before applying to the calibrator wells as described before.[28] We used optical density tracings of fibrin formation and clot lysis performed in 96-well microplates (fibrin generation and clot lysis test) to determine plasma clotting time (CT) and clot lysis time (CLT) as described previously.[29] Briefly, 75 µL of plasma was mixed with 75 µL of start reagent (tissue factor, phospholipids, tissue plasminogen activator, and $CaCl_2$ at final concentrations of 0.5 PM, 4 µM, 50 ng/mL, and 15 mM, respectively) and optical density (405 nM) recorded for 3 hours at 37°C. Start reagent mixture was prepared from commercially obtained ingredients as described.[29] During measurement, we sealed plates to avoid sample dehydration. The first part of the tracing represents fibrin clot formation. We defined CT as the time from reagent addition to half maximal optical density. The second part of the tracing with a decline from maximal to baseline optical density represents clot lysis. We defined CLT as the time between CT and half-maximal lysis. CLT was abrogated in samples from patients on tranexamic acid (CLT > 3 hours). To establish in-house reference ranges, we determined thrombin generation parameters, CT and CLT in nonanticoagulated healthy volunteers (n = 40 for thrombin generation and n = 24 for the fibrin generation and clot lysis test). Male and female donors aged between 20 and 65 and were randomly selected.

2.4 | Statistical analysis

We described continuous variables by central tendency and variability according to the distribution and categorical variables as proportions. We calculated CIs for the primary and safety outcomes using the Wilson method. For comparison of the coagulation parameters of the plasma of the patients at T0 with the plasma of the healthy volunteers, we performed the Mann-Whitney *U* test. For comparison of the intraindividual coagulation parameters over time points T0 and T1, we performed a paired *t*-test analysis. Differences in laboratory values between the group of patients who did achieve effective hemostasis and the group who did not achieve effective hemostasis were evaluated using the Mann-Whitney *U* test.

3 | RESULTS

3.1 | Major bleeding

We included 101 patients with major bleeding with a mean age of 75 years (Table 2). Rivaroxaban was the DOAC that was most frequently used (54%) and the median (interquartile range [IQR]) time since last DOAC intake 10 (6-16) hours. The most common site of bleeding was intracranial (59%), followed by gastrointestinal (27%). Table 3 presents the severity of presentation and course of the 101 patients with major bleeding, stratified for FXa-I and dabigatran. The majority of patients (77%) presented with a category 3 bleeding, which signifies major bleeding presenting with great medical emergency.[26] Of 101 patients, 68 (67%) received a PCC or idarucizumab. In the remaining 33 patients, no PCC or idarucizumab was administered. Of those, 4 patients were considered as a category 4 bleeding, indicating that death was imminent and no lifesaving measures were undertaken, 11 patients were considered as category 1 or 2, in which the treating physician deemed the bleeding not severe enough to warrant urgent hemostatic measures, and 18 in category 3, in which the treating physician decided to take urgent measures (eg, multiple transfusion units, procedures to achieve local hemostasis) but without administration of PCC or idarucizumab.

In total, 68 (67%; 95% CI, 58%-76%) achieved effective hemostasis. Twenty-two (22%; 95% CI, 15%-31%) patients died within 30 days, and in 18 of the 22 patients the cause of death was the initial bleed (17 ICH and 1 peritoneal bleed). Two patients died due to an underlying malignancy, 1 patient died due to multiorgan failure, and in 1 patient the cause was unknown but autopsy showed advanced liver cirrhosis and pulmonary congestion. No patients died of thromboembolic complications. One (1.0%; 95% CI, 0.2%-5.4%) thromboembolic event occurred during the 30-day follow-up period.

3.1.1 | FXa-I–related major bleeding

A total of 76 patients presented with a FXa-I–related major bleeding, of whom 51 (67%) received PCC as a hemostatic agent (Table 3). One patient was mistakenly thought to have a dabigatran-related bleeding, whereas he had a rivaroxaban-related bleeding and therefore first received idarucizumab, immediately followed by PCC after it was learned the patient was on rivaroxaban. The median total dose of administered PCC per patient was 3500 IU (IQR, 3000-4000 IU), corresponding with 50 IU/kg (IQR, 46-50 IU).

Hemostatic efficacy at 24 hours was not assessable in 5 (10%) patients who received PCC due to immediate transfer to another

TABLE 2 Baseline characteristics

	Major bleeding (n = 101)	Urgent intervention (n = 21)
Age, y, mean (SD)	75 (11)	70 (12)
Male sex, n (%)	59 (58)	17 (81)
Weight, kg, mean (SD[a]	77.7 (16)	81.7 (23)
eGFR, n (%)[b]		
>60 mL/min	12 (63)	59 (60)
30-60 mL/min	4 (21)	33 (34)
<30 mL/min	3 (16)	6 (6)
Indication DOAC, n (%)		
Atrial fibrillation	85 (87)	18 (86)
Venous thromboembolism	12 (12)	3 (14)
Other	1 (1)	0
Unknown	3 (3)	0
DOAC type, n (%)		
Apixaban	16 (16)	5 (24)
Dabigatran	25 (25)	5 (24)
Edoxaban	6 (6)	2 (10)
Rivaroxaban	54 (54)	9 (43)
Last DOAC intake, h, median (IQR)[c]	10 (6-16)	10 (8-18)
DOAC levels, median (IQR)[d]		
Apixaban	163 (63-193)	219 (151-219)
Dabigatran	118 (9-133)	42 (8-42)
Edoxaban	163 (128-163)	62 (17-62)
Rivaroxaban	121 (63-279)	138 (84-435)
Concomitant antiplatelet, n (%)		
Acetylsalicylic acid	3	2 (10)
P2Y12 inhibitor	6 (6)	0
Dual antiplatelet therapy	2 (2)	0

Abbreviations: DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

[a]Weight was missing in 28 patients.

[b]e-GFR was measured by the formula of Chronic Kidney Disease Epidemiology Collaboration and was missing in 5 patients.

[c]For major bleeding: n=51, for urgent intevention: n=15.

[d]n = 5 for apixaban, n = 10 for dabigatran, n = 2 for edoxaban, n = 25 for rivaroxaban.

hospital. However, these patients did complete follow-up visits at 30 days by chart review or by telephone. Effective hemostasis was achieved in 32 (70%; 95% CI, 55%-81%) patients (Table 4). Nine (18%; 95% CI, 10%-30%) patients died within 30 days, and 1 (2.0%; 95% CI, 0.3%-10%) patient developed a thromboembolic event. The thromboembolic event was a nonfatal pulmonary embolism, which occurred 10 days after admission in a woman who had been using rivaroxaban for AF and who had been simultaneously treated with fresh frozen plasma, packed cells, and 2 units of platelet transfusions and in whom anticoagulation had not yet been resumed. Rebleeding at the initial bleeding site occurred in 4 patients on days 5, 10, 13, and 24, respectively, 1 of which was provoked by a new head trauma. It is unknown if anticoagulation had been resumed in these patients.

Of the remaining 25 patients with major bleedings who did not receive PCC, effective hemostasis was achieved in 16 of the 25 patients (64%; 95% CI, 45%-80%). At 30 days, 7 (28%; 95% CI, 14%-48%) patients had died and no thromboembolic events occurred.

3.1.2 | Dabigatran-related major bleeding

A total of 25 patients presented with dabigatran-related major bleeding, and 16 (64%) of those patients received idarucizumab as a reversal agent (Table 3). Two patients also received PCC as part of the reversal strategy and 1 patient received only PCC as a reversal agent in a dose of 50 IU/kg. The median total dose of administered idarucizumab was 5 g. Effective hemostasis was achieved in 12 (75%; 95% CI, 51%-90%) patients treated with idarucizumab. The patient who had received PCC as a single reversal agent, had presented with intracerebral bleeding, was rated as poor hemostasis and passed away within 1 day at the hospital. Of the 16 patients, 3 passed away within 30 days (18%; 95% CI, 6%-41%) and no thromboembolic events occurred.

In the 8 patients who did not receive idarucizumab, effective hemostasis was achieved in 4 (50%; 95% CI, 22%-79%), and 3 (38%; 95% CI, 14%-70%) died within 30 days (Table 4).

3.2 | Urgent interventions

We included 21 patients who required to undergo an urgent intervention while on DOAC therapy. Mean (SD) age was 70 (12) years, rivaroxaban was the most commonly used DOAC (43%) (Table 2). The median (IQR) time since last DOAC intake was 10 (8-18) hours. The urgent intervention was a surgery in the operation theater in 11 patients (52%); the remainder underwent other invasive procedures such as chest tube placements (n = 4), nephrostomies (n = 2), lumbar puncture (n = 1), placement of suprapubic catheter (n = 1), and coiling of a chronic hematoma that had occurred after a shoulder fixation. In 19 (90%) patients, PCC or idarucizumab was administered before the urgent intervention (Table 5), and 2 (10%) patients did not receive PCC or idarucizumab. Surgical effective hemostasis was achieved in 20 patients (95%; 95% CI, 77%-99%). In the urgent intervention group, 3 patients (15%; 95% CI, 5%-36%) passed away within 30 days. Two patients died due to an underlying sepsis, and 1 patient died due to an ischemic stroke. One (5%; 95% CI, 1%-23%) thromboembolic event occurred in 1 patient.

3.2.1 | Urgent intervention while on FXa-I

A total 16 of the 21 patients (76%) presented with an indication for urgent intervention while on a FXa-I , of whom 14 (88%) received

TABLE 3 Details of major bleeding

At presentation	Total (n = 101)	FXa-I (n = 76)	Dabigatran (n = 25)
Site of the bleeding, n (%)			
Gastrointestinal	27 (27)	21 (28)	6 (24)
Intracranial	60(59)	45 (59)	15 (60)
Other	14(14)	10 (13)	4 (16)
Bleeding due to trauma, n (%)	37 (39)	28 (37)	9 (36)
Hemoglobin at presentation (mmol/L), mean (SD)	7.0 (2.1)	7.0 (2.1)	7.3 (1.3)
Presentation severity, n (%)[d]			
Category 1	1 (1)	1 (1)	0
Category 2	16 (16)	12 (16)	4 (16)
Category 3	78 (77)	58 (76)	20 (80)
Category 4	6 (6)	5 (7)	1 (4)
Administration of reversal agent, n (%)	68 (67)	51 (67)	17 (68)
PCC, n (%)	54 (54)	51 (67)	3 (12)
Total dose PCC, IU/kg, median (IQR)	3500 (3000-4000)	3500 (3000-4000)	3000 (NA)
Dose of PCC, IU, median (IQR)	50 (37.5-50)	50 (46-50)	28 (NA)
Idarucizumab, n (%)	16 (16)	1 (1)	16 (64)
Dose of idarucizumab, g, median (IQR)	5 (5-5)	5 (NA)	5 (5-5)
Dose of idarucizumab, median (IQR)	5 (5-5)	5 (NA)	5 (5-5)
Tranexamic acid, n (%)	15 (15)	12 (16)	3(12)
Fresh frozen plasma, n (%)	5 (5)	4 (5)	1 (4)
Procedure to control bleeding, n (%)			
Surgical intervention	18 (18)	13 (17)	5(20)
Endoscopic intervention	20 (20)	16 (21)	4(16)
Radiologic intervention	2 (2)	1 (1)	1(4)
Other	1 (1)	NA	1(4)
Erythrocytes transfusion, n (%)	31 (31)	23 (30)	8 (32)
≤2 units	10 (10)	8 (11)	2(8)
>2 units	20 (20)	14 (18)	6(24)
Platelet transfusion, n (%)	7 (7)	7 (9)	0 (0)
Clinical course			
Duration of hospitalization, mean (SD)	7 (3-14)	10 (9)	10 (11)
ICU admission, n (%)	35 (37)	25 (33)	10 (40)
Duration ICU admission, d, mean (SD)	2.4 (5.4)	2.3 (5.3)	2 (5)
Clinical course severity[d]			
Category 1, n (%)	5 (5)	3 (4)	2 (8)
Category 2, n (%)	36 (36)	26 (34)	10 (40)
Category 3, n (%)	47 (47)	39 (51)	8 (32)
Category 4, n (%)	3 (3)	6 (8)	4 (16)
Not assessable	0	0	1

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable; SD, standard deviation.

[a]Systolic blood pressure was missing in 8 patients.

[b]Pulse was missing in 11 patients.

[c]Was missing in 5 patients.

[d]Subclassification for ISTH major bleeding according to the severity of bleeding, previously described in methods section of this paper.

TABLE 4 Outcome of major bleeding

	FXa-I (n = 76)[a]		Dabigatran (n = 25)[a,b]	
	PCC (n = 51)	No reversal (n = 25)	Idarucizumab (n = 16)	No reversal (n = 8)
Primary outcome, n (%, 95% CI)				
Effective hemostasis after 24 h	32 (70%, 55-81)	16 (64%, 45-80)	12 (75%, 51-90)	4 (50%, 22-79)
Safety outcomes, n (%, 95% CI)				
30-d mortality rate	9 (18%, 10-30)	7 (28%, 14-48)	3 (18%, 6-41)	3 (38%, 14-70)
30-d thromboembolic rate	1 (2.0%, 0.3-10)	0	0	0

Abbreviations: FXa-I, factor Xa inhibitor; PCC, prothrombin complex concentrate.

[a]Due to transfer to other hospitals, effective hemostasis could not be assessed in 5 patients; all 5 were in the PCC group.

[b]Two patients received both idarucizumab and PCC as a reversal agent, and 1 patient only received PCC for dabigatran reversal. The patient's outcomes are not presented in this table but are described in the text.

TABLE 5 Details of urgent interventions

Specification urgent intervention at presentation	Total (n = 21)	FXa-I (n = 16)	Dabigatran (n = 5)
Urgent intervention, n (%)			
Surgery	11 (52)	8 (50)	3 (60)
Other procedure	10 (48)	8 (50)	2 (40)
Administration of reversal agent	19 (91)	14 (88)	5 (100)
PCC, n (%)	14 (67)	14 (88)	0
Dose of PCC, IU, median (IQR)	2500 (1438-4000)	2500 (1438-4000)	NA
Total dose PCC, IU/kg, median (IQR)	45 (25-50)	45 (25-50)	NA
Idarucizumab, n (%)	5 (24)	0	5 (100)
Dose of idarucizumab, g, median (IQR)	5 (5-5)	NA	5 (5-5)
Erythrocytes transfusion, n (%)	3 (14)	1 (6)	2 (40)
≤2 units	1 (5)	NA	1 (20)
>2 units	2 (10)	1 (6)	1 (20)
Specification urgent intervention during course			
Duration of hospitalization, mean (SD)	18 (12)	11 (7-30)	30 (16-32)
ICU admission, n (%)[a]	12 (60)	9 (56)	3 (60)
Duration of ICU admission, d, mean (SD)	6 (10)	5 (3-18)	4 (4-6)

Abbreviations: FXa-I, factor Xa inhibitor; IQR, interquartile range; NA, not applicable; PCC, prothrombin complex concentrate; SD, standard deviation.

[a]1 missing value.

PCC as a reversal agent. Surgical effective hemostasis was achieved in all 14 patients (100%; 95% CI, 79%-100%) (Table 6). Of the 14 patients, 1 (7%; 95% CI, 1%-32%) patient passed away within 30 days, including 1 (7%; 95% CI, 1%-32%) patient on rivaroxaban for AF who died from an ischemic stroke 7 days after administration of PCC in a dose of 50 IU/kg; it is unclear whether anticoagulation had been resumed. This was the only thromboembolic event corresponding with a 30-day thromboembolic rate of 7% (95% CI, 1%-32%).

Of the 2 patients who did not receive PCC, 1 (50%; 10%-91%) patient on rivaroxaban had major bleeding within 7 days after the

TABLE 6 Outcomes of urgent interventions

	FXa-I (n = 16)		Dabigatran (n = 5)
	PCC (n = 14)	No reversal agent (n = 2)	Idarucizumab (n = 5)
Primary outcome, n (%, 95% CI)			
Surgical effective hemostasis after 7 d	14 (100, 79-100)	1 (50, 10-91)	5 (100, 57-100)
Safety outcomes, n (%, 95% CI)			
30-d mortality rate	1 (7, 1-32)	1 (50, 10-91)	1 (20, 4-62)
30-d thromboembolic rate	1 (7, 1-32)	0	0

Abbreviations: CI, confidence interval; FXa-I, factor Xa inhibitor; PCC, prothrombin complex concentrate.

surgical procedure, 3 days after anticoagulation was resumed. The other patient died within 1 day after admission; the death was due to sepsis. No thromboembolic events were reported.

3.2.2 | Urgent intervention while on dabigatran

All 5 (100%) patients presenting with an indication for urgent intervention while on dabigatran were treated with idarucizumab before the intervention took place. Surgical effective hemostasis rate was achieved in all patients (100%; 95% CI, 57%-100%) (Table 6). No thromboembolic events occurred, and 1 (20%; 95% CI, 54%-62%) patient died.

3.3 | Laboratory outcomes

3.3.1 | Baseline DOAC levels

Major bleeding

We were able to collect samples for analysis of anti-Xa levels in 30 patients (30%) using FXa-I and dabigatran levels in 7 patients (7%) taking dabigatran who presented with major bleeding. Of the 30 patients in whom anti-Xa levels were measured, 5 (17%) had anti-Xa levels <50 ng/mL, and of the 7 patients in whom dabigatran levels were measured, 2 (29%) had dabigatran levels <50 ng/mL. Rivaroxaban levels in samples taken at presentation (n = 24) ranged between 0 and 542 ng/mL, apixaban levels (n = 4) ranged between 38 and 200 ng/mL, and edoxaban levels (n = 2) ranged between 128 and 197 ng/mL. Patients on dabigatran (n = 7) had plasma levels from 1 to 240 ng/mL. Median drug levels are presented in Table 2.

Urgent interventions

In patients who presented with an indication for urgent intervention while on a DOAC, we were able to collect samples for analysis of anti-Xa levels of 9 (43%) patients taking FXa-I and dabigatran levels in 2 (40%) patients taking dabigatran. Of the 9 patients in whom anti-Xa levels were measured, 2 (22%) were <50 ng/mL, and of the 2 patients in whom dabigatran levels were measured, 1 (50%) was <50 ng/mL. Rivaroxaban levels in samples taken at presentation (n = 5) ranged between 30 and 452 ng/mL, apixaban levels (n = 2) and edoxaban levels (n = 2) ranged between 151 and 286 ng/mL and 17 and 106 ng/mL, respectively. Patients on dabigatran (n = 2) had plasma levels from 8 to 75 ng/mL.[30] Median drug levels are presented in Table 2.

3.3.2 | Baseline thrombin generation in patients with DOAC-related emergencies

Figure 1A shows the tissue factor–triggered thrombin generation (CAT assay) in samples from DOAC-treated patients (patients with bleeding and urgent interventions combined) in comparison to the healthy volunteers. Lag time showed a significant ($P < .0001$) prolongation in almost all samples up to 700% of normal. DOAC level was plotted against CAT lag time in Figure 1B. The ETP between samples from DOAC-treated patients and healthy volunteers at baseline showed no significant difference for both FXa-I– ($P = .06$) and dabigatran- ($P = .09$) treated patients. The thrombin peak was significantly reduced in patients on a FXa-I ($P < .0001$) but not in those on dabigatran ($P = .75$). CLT was abrogated in 8 samples from patients on tranexamic acid (CLT > 3 hours). CT, in accordance with CAT lag time, was clearly prolonged in both FXa-I and dabigatran samples ($P = .004$) (Figure 1A). In the analyzed DOAC samples, clot stability varied from slightly reduced to enhanced in comparison with the control plasma. Most patients, however, had a CLT within the normal range (Figure 1A).

3.3.3 | Thrombin generation in patients treated with PCC for a FXa-I–related major bleeding

We obtained plasma from 19 (37%) of 51 patients receiving PCC for treatment of major bleeding. In Figure 2, parameters for thrombin generation (lag time, peak thrombin generation, ETP), CT, and CLT are shown for the 19 patients receiving PCC in management of bleeding. Immediately after administration of PCC, laboratory analysis showed normalization of CAT peak and ETP to levels exceeding the reference.

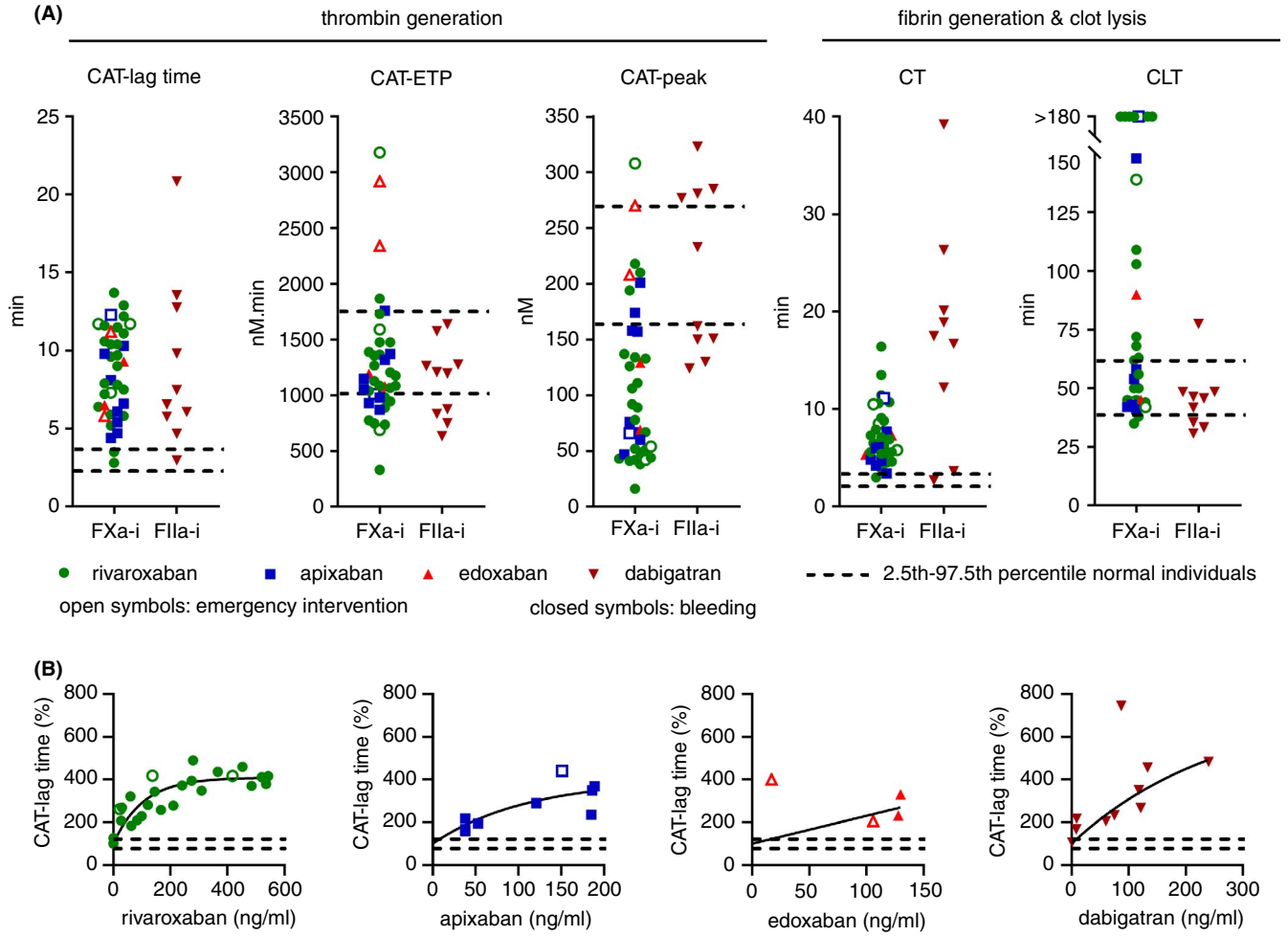

FIGURE 1 A, Coagulation parameters in DOAC-treated patients at presentation. Patients on FXa-I: rivaroxaban, n = 25 (green circles); apixaban, n = 9 (blue squares); edoxaban, n = 4 (red upward triangles). Patients on dabigatran, n = 10 (dark red downward triangles). Open circles, urgent intervention patients. Closed circles, patients presented with major bleeding. The 2.5th-97.5th percentile interval for normal plasma samples (n = 40 for thrombin generation and n = 24 for the fibrin generation & clot lysis test) is represented as a gray bar. B, CAT lag time as function of DOAC concentration. The data are expressed as a percentage of the average normal value. CAT, calibrated automated thrombography (tissue factor–triggered thrombin generation); CLT, clot lysis time; CT, clotting time; ETP, endogenous thrombin potential; FXa-I, factor Xa inhibitor; lag, lag time; peak, thrombin peak

We obtained samples at time points T0 and T1 in 13 patients and the full series of samples (T0, T1, and T2) in 9 patients. Mean ETP values increased with 96% immediately after PCC administration from 1108 nM.Min at T0 to 2275 nM.Min at T1 (P = .001) with 2 patients (18%) at T0 and 11 patients (79%) at T1 exceeding the upper limit of the ETP reference range. Mean (SD) ETP at T2 was 2539 (699) nM.Min (n = 14). For peak thrombin (n = 13), comparable results were observed with an increase of 113% from T0 to T1 (P = value .001). For CLT analysis (n = 9), mean values increased significantly from T0 to T1 (P = .014), indicating more stable clots after the administration of PCC.

3.4 | Association between clinical and laboratory outcomes

We did not observe differences in anti-Xa levels or thrombin generation parameters between patients with or without effective hemostasis at any time point. This is illustrated by the wide distribution of laboratory values in Figure 2, in which gray circles represent patients with effective hemostasis and black circles represent patients with poor hemostasis. Laboratory values, stratified for effective hemostasis, are presented in more detail in Figure 3. The thrombin generation parameters of the patient who developed VTE 10 days after administration of PCC did not exceed the reference range of ETP or peak thrombin for nonanticoagulated healthy volunteers.

4 | DISCUSSION

In this study, 67% of patients presenting with DOAC-related major bleeding achieved effective hemostasis. For patients with a FXa-I–related major bleeding (n = 76), two thirds of the patients received PCC as a hemostatic agent and effective hemostasis was

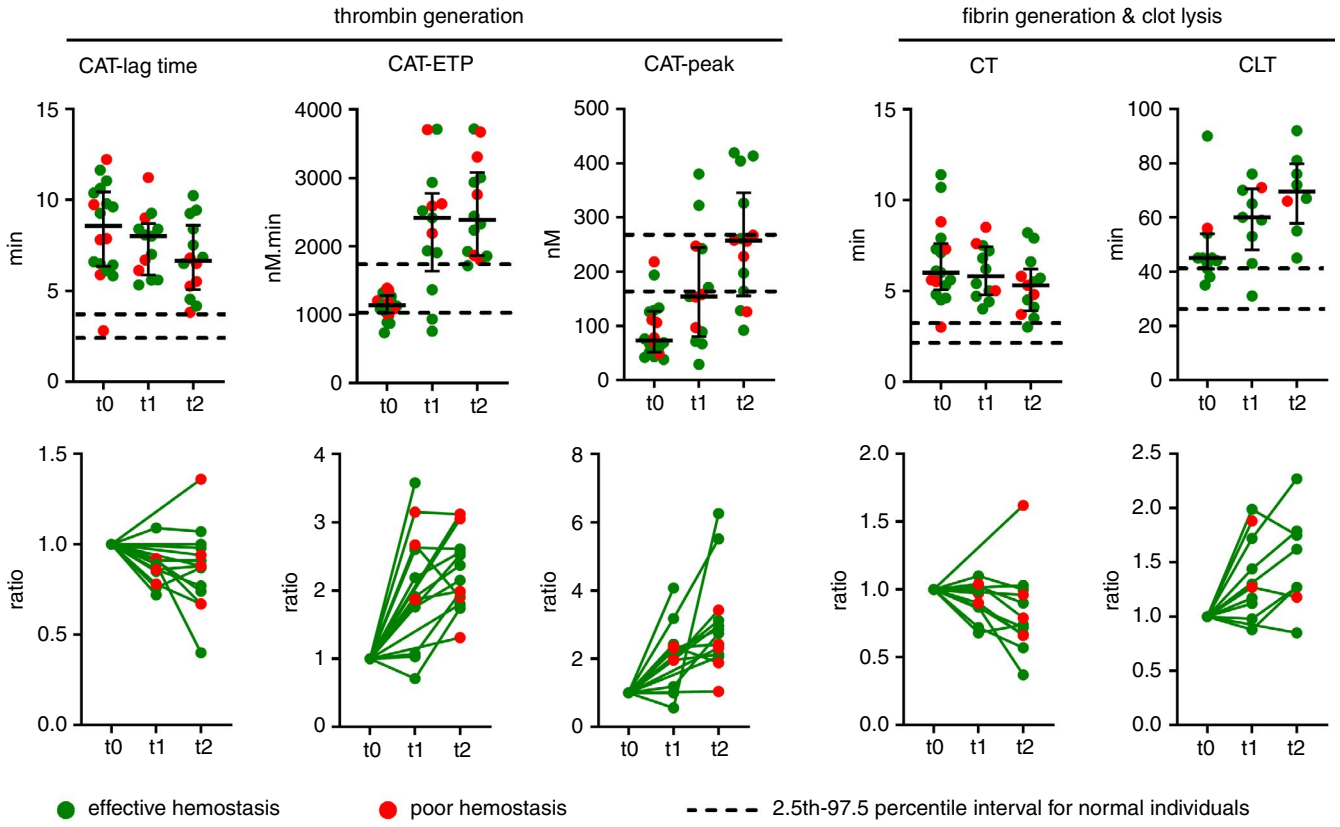

FIGURE 2 Coagulation parameters in patients with a FXa-I–related major bleeding treated with PCC. Plasma samples were taken at presentation (T0), 15-30 minutes after administration of PCC (T1) and 4-8 h after presentation (T2). Patients with effective hemostasis are represented as green circles, and those with poor hemostasis are in red. Clot lysis evaluation was omitted in samples from patients on tranexamic acid. Upper graphs: absolute value of assay parameter with dotted lines delimiting the 2.5th-97.5th percentile interval for normal plasma samples (n = 40 for thrombin generation and n = 24 for the fibrin generation and clot lysis test). Bottom graphs: data represented as ratio of T0 value. FXa-I, factor Xa inhibitor; PCC, prothrombin complex concentrate

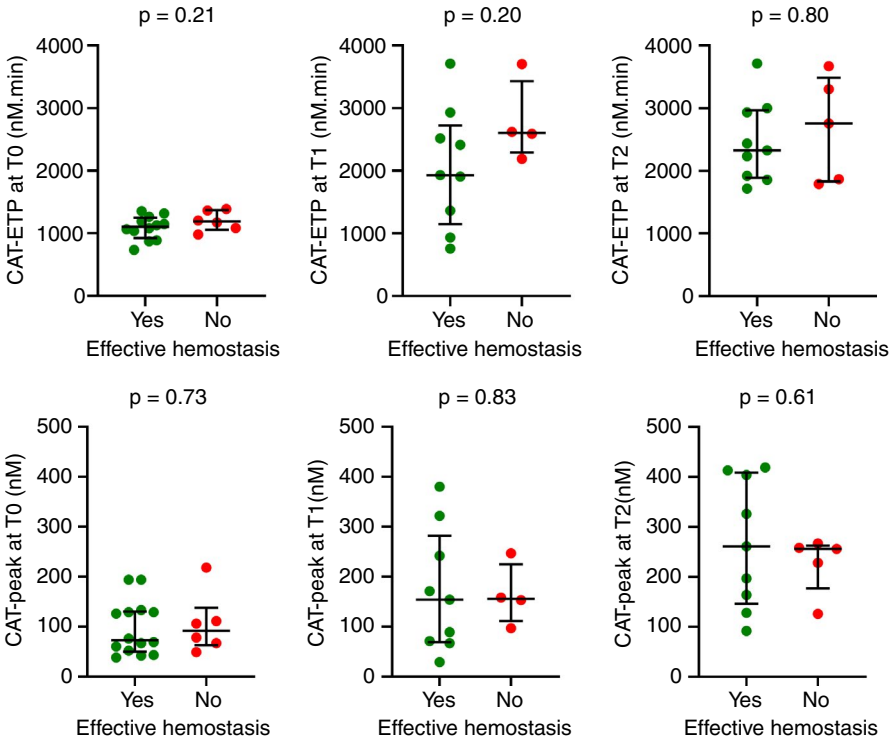

FIGURE 3 Median thrombin generation parameters for patients on FXa-Is at different time points, stratified by effective hemostasis. The main horizontal line represents the median value and the lower and upper limit represent the interquartile ranges. Patients with effective hemostasis are represented as green circles and those with poor hemostasis are in red. FXa-I, factor Xa inhibitor

70% (95% CI, 55%-81%) in those patients. Taking into consideration the low observed thromboembolism (2%; 95% CI, 0.3%-10%) incidence within 30 days, a high-dose PCC could be a reasonable option for FXa-I–related major bleeding, with laboratory samples confirming a swift increase in thrombin generation after administration of PCC. For the patients with dabigatran-related major bleeding (n = 25), 64% received idarucizumab as a reversal agents and effective hemostasis was 75% (95% CI, 51%-90%) in those patients. DOAC blood levels varied widely at presentation of the emergency, but did not seem to be associated with the clinical outcome.

Of the patients presenting with the need for an urgent intervention while on a DOAC (n = 21), 95% achieved surgical effective hemostasis. For the patients with the need for an urgent intervention while on a FXa-I (n = 16), PCC was administered in 14 (88%) patients. Effective surgical hemostasis was achieved in all 14 patients receiving PCC. Idarucizumab was administered in all 5 patients presenting with the need for an urgent intervention while on dabigatran and all patients achieved effective surgical hemostasis.

The observed 70% effective hemostasis and the low thromboembolic events rate in the group with FXa-I–related major bleeding receiving PCC is in line with previous findings of other prospective cohort studies showing a pooled effective hemostasis rate of 69% (95% CI, 61%-76%) according to the ISTH definition.[21,22]

The results of the present study can also be related to the trials that led to regulatory approval of PCC for VKA reversal, idarucizumab for dabigatran reversal, and andexanet alfa for apixaban and rivaroxaban reversal.[13,23,31] In the single-armed study leading to approval of idarucizumab for reversal of dabigatran (REVERSE-AD), effective hemostasis was not determined. However, 68% of the patients had confirmed bleeding cessation within 24 hours.[13] In the trial leading to approval of PCC for reversal of VKA and in the single-armed cohort study leading to approval of andexanet alfa (ANNEXA-4) for specific reversal of FXa-I, effective hemostasis was achieved in 72% and 82%, respectively.[23,31] The achieved 70% (95% CI, 55%-81%) effective hemostasis in our patients managed with PCC for FXa-I related major bleeding is in line with those studies.[13,23,31] Thromboembolic events occurred in 4.8% of the patients in the REVERSE-AD cohort, in 7.8% of the patients in trial leading to approval of PCC for reversal of VKA in the United States, and in 10% of the patients in the ANNEXA-4 cohort. Our observed 2% (95% CI, 0.3%-10%) thromboembolic rate is, again, in line with those studies. In this study, we did not account for the competing risk of death for thrombosis, and this may have led to an underestimation of the thromboembolic events.

The 30-day mortality of DOAC emergencies was substantial, irrespective of the bleeding management, which could partially be explained by the large proportion of intracranial hemorrhages in this cohort. This incidence is again in line with other oral anticoagulation–related major bleeding cohorts managed with their specific reversal agents. This likely suggests that most harm of the bleeding occurs before presentation at the hospital in a large proportion of patients with oral anticoagulant–related major bleeding. The mortality benefit of any reversal strategy is limited in those patients and reinforces the demand for a randomized controlled trial to understand the additional value of any reversal agent on top of supportive measures.[13,23,31]

Our observed surgical effective hemostasis rate after treatment with PCC is high and similar to the rate observed in an Israeli retrospective study in which they included more severe urgent interventions than we did in our cohort.[32] Thromboembolic and mortality rates at 30 days are similar. However, when making this indirect comparison, it needs to be kept in mind that for both cohorts different definitions for the primary outcome effective hemostasis were applied.[32]

Of interest, in spite of similar effective hemostasis and thromboembolism, the median administered dose of PCC in our cohort was twice as high (50 vs. 25 IU/kg) than in the other 2 cohorts reporting effective hemostasis.[21,22] This raises important questions on the optimal PCC dose. The rationale for our dose was based on studies in healthy volunteers who received PCC at the time of expected peak blood levels. In these studies only a 50 IU/kg dose of PCC fully restored ETP, whereas doses of 25 and 37.5 IU/kg increased ETP but not to preanticoagulation levels.[16] In contrast to the healthy volunteers study, most patients in this cohort received PCC well after the expected peak blood level, at which time a lower than 50 IU/kg dose may be sufficient. Moreover, it needs to be taken into account that in all 3 of these studies in bleeding patients other hemostatic measures, along with administration of PCC, were also taken. If PCC will continue to be used as a hemostatic agent for FXa-I–related emergencies, further studies into the optimal PCC dosing is warranted.

Parameters of thrombin generation, mainly lag time and peak thrombin, show significant differences in patients treated with DOACs compared with normal subjects with lag time as the most sensitive parameter. Moreover, in patients treated with PCC for FXa-I emergencies, our results demonstrate a correction in thrombin generation parameters after administration, particularly in peak thrombin and ETP, confirming the results of in vitro experiments as well as studies in healthy nonbleeding volunteers.[16,33,34]. Increased thrombin generation after PCC administration coincided with increased clot stability (elongated CLT), in accordance with previous in vitro observations.[29] These findings are difficult to interpret as the effect of bleeding on thrombin generation is unknown and as a universal reference range for thrombin generation has never been established. Our results do not suggest a relationship between these coagulation indices and severity of bleeding or complications. It may be so that such coagulation tests cannot sufficiently reflect local hemostasis at the site of injury, or this finding could be a consequence of the lack of validation of our primary outcome, as stated below. Future research in a larger setting should investigate the role of coagulation parameters for management and predicting outcomes of DOAC-related bleeding.

The observational design of this study is the main limitation for the interpretations of our results. As the management of these

patients was left to the discretion of the treating physician, clinical outcomes were subject to confounding by indication. Therefore, we made no head-to-head comparison between the patients who received PCC and the ones who did not. Nevertheless, this design is inherent to the study subject as reversal agent studies tend to be single-arm studies and have never been compared to placebo before.[13,31] Second, there are some limitations regarding the applied ISTH definition for effective hemostasis. Most importantly, this definition is a clinical score and has some subjective elements, such as evaluation of neurological scoring (intracerebral bleeding) or evaluating of pain and swelling (musculoskeletal bleeding). Furthermore, other aspects, such as the hemoglobin drop over time, lack specificity and are influenced by other factors than cessation of bleeding such as hydration status at presentation. Nevertheless, a validation study of this score demonstrated acceptable interobserver reliability, and the interpretation of the score (effective vs ineffective hemostasis) had substantial agreement with the subjective clinical opinion of the treating physician. Therefore, in spite of these limitations, the ISTH definition probably remains the best score to evaluate the outcome of major bleeding.[35]

Additionally, the limited sample size leads to lack of statistical power, which precludes multivariate regression analysis for determinants that independently predict effective hemostasis or thromboembolism, including the use of hemostatic agents. Finally, we cannot rule out a selection bias in this cohort, as we would have expected more gastrointestinal bleeding for a consecutively including cohort and may have missed some patients with gastrointestinal bleeding that were not notified to the study team. Along with the potential selection bias, the fact that 4 of the 5 participating centers are academic neurological centers likely explains the high proportion of intracranial bleeding in our cohort.

Our study further supports that PCC, in addition to other hemostatic measures, leads to substantial proportions of effective hemostasis and may possibly be effective in the management of FXa-I–related major bleeding or urgent interventions. We believe PCC is safe due to the low observed thromboembolic incidence; however, we acknowledge the high mortality rate and the need for further exploration on the reasons for death, before classifying PCC as a safe agent. Whether the results obtained with PCC are similar to those obtained by the specific reversal agent andexanet alfa would need to be answered by a randomized controlled trial. Regulatory approval of andexanet alfa by the FDA and EMA was conditional upon further studies into efficacy and safety of reversal of FXa-I.[14,36] Currently, a randomized controlled trial investigating the efficacy and safety of andexanet alfa compared to usual care for patients presenting with a FXa-I–related intracranial hemorrhage, is recruiting and will inform the medical community which strategy should best be used in the management of FXa-I related emergencies (trialregister.gov; NCT03661528).

ACKNOWLEDGMENTS

The study was funded by ZonMw (Grant No. 836021017). Sanquin Blood Supply and Daiichi Sankyo provided additional financial support for conducting the study. The sponsor had no influence on the study design or conduct, the collection and analyses of data, and the final manuscript writing and approval.

AUTHOR CONTRIBUTIONS

RB contributed to collection of data, data analysis, and drafting the manuscript; AR contributed to drafting the manuscript; HB contributed to analyzation of the blood samples, data analysis, the figures, and drafting the manuscript; MB contributed to the study concept, drafting the study protocol, and collection of data; EH contributed to collection of data and drafting the manuscript; MZ contributed to analyzation of the blood samples and drafting the manuscript; BH contributed to data analysis and drafting the manuscript; PW contributed to collection of data and drafting the manuscript; RO contributed to collection of data and drafting the manuscript; HC contributed to collection of data and drafting the manuscript; MK contributed to collection of data and drafting the manuscript; SM contributed to the study concept and drafting the manuscript; KM contributed towards collection of data and drafting the manuscript; MC contributed to the study concept, drafting the study protocol, and drafting the manuscript.

Additional supporting information may be found online in the Supporting Information section at the end of the article.

ORCID

Roisin Bavalia https://orcid.org/0000-0002-1806-1050
Saskia Middeldorp https://orcid.org/0000-0002-1006-6420

TWITTER

Saskia Middeldorp @MiddeldorpS

REFERENCES

1. Chai-Adisaksopha C, Hillis C, Isayama T, Lim W, Iorio A, Crowther M. Mortality outcomes in patients receiving direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Thromb Haemost. 2015;13(11):2012–20.
2. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood. 2014;124(15):2450–8.
3. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
6. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
7. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. Am J Med. 2015;128(12):1300–1305.e1302.
8. van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968–75.

9. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. 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(9921):955–62.
10. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–52.
11. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893–962.
12. Boehringer Ingelheim International GmbH. Pradaxa® (dabigatran etexilate) Available at: https://www.ema.europa.eu/documents/overview/pradaxa-epar-summary-public_en.pdf. In. Vol 20192018.
13. Pollack Jr CV, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for dabigatran reversal - full cohort analysis. N Engl J Med. 2017;377(5):431–41.
14. Portola pharmaceuticals I. Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo): US Prescribing Information. www.fda.gov/medwatch. Published 2018. Accessed.
15. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J. 2013;34(27):2094–106.
16. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Büller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124(14):1573–9.
17. Levi M, Moore KT, Castillejos CF, Kubitza D, Berkowitz SD, Goldhaber SZ, et al. 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(9):1428–36.
18. Cheung YW, Barco S, Hutten BA, Meijers JC, Middeldorp S, Coppens M. In vivo increase in thrombin generation by four-factor prothrombin complex concentrate in apixaban-treated healthy volunteers. J Thromb Haemost. 2015;13(10):1799–805.
19. Barco S, Picchi C, Trinchero A, Middeldorp S, Coppens M. Safety of prothrombin complex concentrate in healthy subjects. Br J Haematol. 2017;176(4):664–6.
20. Piran S, Khatib R, Schulman S, Majeed A, Holbrook A, Witt DM, et al. Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. Blood Adv. 2019;3(2):158–67.
21. Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. Thromb Haemost. 2018;118(5):842–51.
22. Majeed A, Agren A, Holmstrom M, Bruzelius M, Chaireti R, Odeberg J, et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017;130(15):1706–12.
23. Sarode R, Milling Jr TJ, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013;128(11):1234–43.
24. Khorsand N, Majeed A, Sarode R, Beyer-Westendorf J, Schulman S, Meijer K. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. J Thromb Haemost. 2016;14(1):211–4.
25. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692–4.
26. Bleker SM, Brekelmans MPA, Eerenberg ES, Cohen AT, Middeldorp S, Raskob G, et al. Clinical impact of major bleeding in patients with venous thromboembolism treated with factor Xa inhibitors or vitamin K antagonists. Thromb Haemost. 2017;117(10):1944–51.
27. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010;8(1):202–4.
28. Kopatz WF, Brinkman HJM, Meijers JCM. Use of DOAC Stop for elimination of anticoagulants in the thrombin generation assay. Thromb Res. 2018;170:97–101.
29. Helin TA, Zuurveld M, Manninen M, Meijers JCM, Lassila R, Brinkman HJM. Hemostatic profile under fluid resuscitation during rivaroxaban anticoagulation: an in vitro survey. Transfusion. 2018;58(12):3014–26.
30. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate–a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103(6):1116–27.
31. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. N Engl J Med. 2019;380(14):1326–35.
32. Barzilai M, Kirgner I, Steimatzky A, Salzer Gotler D, Belnick Y, Shacham-Abulafia A, et al. Prothrombin complex concentrate before urgent surgery in patients treated with rivaroxaban and apixaban. Acta Haematol. 2019;1–6.
33. Dinkelaar J, Molenaar PJ, Ninivaggi M, de Laat B, Brinkman HJ, Leyte A. In vitro assessment, using thrombin generation, of the applicability of prothrombin complex concentrate as an antidote for Rivaroxaban. J Thromb Haemost. 2013;11(6):1111–8.
34. Dinkelaar J, Patiwael S, Harenberg J, Leyte A, Brinkman HJ. Global coagulation tests: their applicability for measuring direct factor Xa- and thrombin inhibition and reversal of anticoagulation by prothrombin complex concentrate. Clin Chem Lab Med. 2014;52(11):1615–23.
35. Abdoellakhan RA, Beyer-Westendorf J, Schulman S, Sarode R, Meijer K, Khorsand N. Method agreement analysis and interobserver reliability of the ISTH proposed definitions for effective hemostasis in management of major bleeding. J Thromb Haemost. 2019;17(3):499–506.
36. Netherlands P. Ondexxya. 2019. [Updated 2019 May 8; cited 2019 Nov 21]. Available from http://ec.europa.eu/health/documents/community-register/html/h1345.htm

How to cite this article: Bavalia R, Abdoellakhan R, Brinkman HJM, et al. Emergencies on direct oral anticoagulants: Management, outcomes, and laboratory effects of prothrombin complex concentrate. *Res Pract Thromb Haemost*. 2020;4:569–581. https://doi.org/10.1002/rth2.12336