Original Article

DOI: 10.14235/bas.galenos.2025.27048
Bezmialem Science 2026;14(2):172-179

Role of Prothrombin Complex Concentrates in Reversal of Direct Oral Anticoagulant Effects

Yeni Nesil Oral Antikoagülan Etkilerinin Tersine Çevrilmesinde Protrombin Kompleksi Konsantrelerinin Rolü

Gökhan ERSUNAN[1], İsmail ATAŞ[1], Mümin Murat YAZICI[1], Enes GÜLER[2], Özlem BİLİR[1]

[1]Recep Tayyip Erdoğan University Training and Research Hospital, Department of Emergency Medicine, Rize, Türkiye
[2]Kırklareli University Training and Research Hospital, Department of Emergency Medicine, Kırklareli, Türkiye

ABSTRACT

Objective: The aim of this study is to evaluate the efficacy and safety of four-factor prothrombin complex concentrate in reversing the anticoagulant effect in patients presenting to the emergency department with bleeding associated with direct oral anticoagulants.

Methods: This single-center, retrospective study evaluated the dosage and efficacy of prothrombin complex concentrate in reversing the anticoagulant effect in patients presenting to the emergency department of a tertiary hospital due to bleeding associated with direct oral anticoagulants or due to elevated international normalized ratio prior to an emergency procedural intervention associated with direct oral anticoagulants.

Results: Of the 20 participants, 65% were 80 years of age or older. The most common presenting complaints were gastrointestinal and musculoskeletal bleeding. The participants received a total of 34 doses (500 IU/20 mL) of prothrombin complex concentrate, and pre- and post-treatment coagulation test results showed significant improvement. However, no significant relationship was observed between hospital outcome (i.e., death or discharge) and the treatment protocols. Four patients developed thromboembolic events after treatment, and two of these had received more than one prothrombin complex concentrate dose.

Conclusion: Four-factor prothrombin complex concentrates are useful adjuncts for the urgent reversal of the direct oral anticoagulants-associated anticoagulant effects, particularly

ÖZ

Amaç: Bu çalışmanın amacı, yeni nesil oral antikoagülanlara bağlı kanamalarda dört faktörlü protrombin kompleks konsantresinin acil servisteki hastalarda antikoagülan etkisini tersine çevirmedeki etkinliğini ve güvenliğini değerlendirmektir.

Yöntemler: Bu tek merkezli, retrospektif çalışma, yeni nesil oral antikoagülanlarla ilişkili kanama nedeniyle veya yeni nesil oral antikoagülanlarla ilişkili acil prosedürel işlem öncesi uluslararası normalleştirilmiş oran yüksekliği saptanması üzerine üçüncü basamak bir hastanenin acil servisine başvuran hastalarda protrombin kompleks konsantresinin antikoagülan etkisini tersine çevirmedeki dozajını ve etkinliğini değerlendirmiştir.

Bulgular: Yirmi katılımcının %65'i 80 yaş ve üzerindeydi. En sık görülen şikayetler gastrointestinal ve kas-iskelet sistemi kanamalarıydı. Katılımcılara toplam 34 doz (500 IU/20 mL) protrombin kompleks konsantresi verildi ve tedavi öncesi ve sonrası pıhtılaşma testi sonuçları önemli bir iyileşme gösterdi. Ancak, hastane sonlanımı (yani ölüm veya taburculuk) ile tedavi protokolleri arasında önemli bir ilişki gözlenmedi. Dört hastada tedaviden sonra tromboembolik olay gelişti ve bunlardan ikisi birden fazla protrombin kompleks konsantresi dozu almıştı.

Sonuç: Dört faktörlü protrombin kompleks konsantreleri, özellikle bu tür müdahalelere ihtiyaç duyanların çoğunluğunu oluşturan geriatrik hastalarda, yeni nesil oral antikoagülanlarla ilişkili antikoagülan etkilerin acil olarak tersine çevrilmesi için

Address for Correspondence: İsmail Ataş MD, Recep Tayyip Erdoğan University Training and Research Hospital, Department of Emergency Medicine, Rize, Türkiye
E-mail: drismailatas@gmail.com
ORCID IDs of the authors: G.E.: 0000-0002-4523-0294, İ.A.: 0000-0001-6723-8564, M.M.Y.: 0000-0003-1957-7283, E.G.: 0000-0003-4926-0332, Ö.B.: 0000-0001-9016-1665

Cite this article as: Ersunan G, Ataş İ, Yazıcı MM, Güler E, Bilir Ö. Role of prothrombin complex concentrates in reversal of direct oral anticoagulant effects. Bezmialem Science. 2026;14(2):172-179

Received: 10.11.2025
Accepted: 03.12.2025
Epub: 01.04.2026
Published date: 20.04.2026

ABSTRACT

in geriatric patients who comprise the majority of those requiring such interventions. Nonetheless, clinicians should be aware that the risk of thromboembolism may increase with repeated dosing.

Keywords: Factor Xa inhibitors, direct thrombin inhibitors, anticoagulant reversal

ÖZ

yararlı yardımcı maddelerdir. Bununla birlikte, klinisyenler tekrarlanan dozlarla tromboemboli riskinin artabileceğini bilmelidir.

Anahtar Kelimeler: Faktör Xa inhibitörleri, doğrudan trombin inhibitörü, antikoagülan tersine çevirme

Introduction

Anticoagulants are a group of drugs with a wide range of indications, including atrial fibrillation, venous thromboembolism, and thromboprophylaxis, in patients at risk of thrombosis (1). The use of direct thrombin inhibitors, such as dabigatran, or direct factor Xa inhibitors, such as rivaroxaban, apixaban, and edoxaban, has become preferable due to problems in coagulation monitoring and dose adjustment as well as the drug-drug and diet-drug interactions of vitamin K antagonists, such as warfarin (2). Compared with warfarin, the new generation of oral anticoagulants has a lower risk of life-threatening bleeding (3). Unlike vitamin K antagonists, direct oral anticoagulants (DOAC) do not require monitoring. Nonetheless, patients should be informed of conditions that may pose a bleeding risk as well as the signs and symptoms of bleeding. In particular, the use of drugs that predispose patients to bleeding, such as drugs used to treat uncontrolled systemic hypertension (systolic blood pressure >160 mmHg), drugs used to treat impaired renal function, antiplatelet therapy, non-steroidal anti-inflammatory drugs (NSAID), and selective serotonin reuptake inhibitors (SSRI), should be restricted (4).

Appropriate strategies must be established to prevent bleeding due to anticoagulation and to manage bleeding in the event of bleeding. To determine a treatment, it is important to understand the severity and extent of the bleeding. Bleeding that is mostly self-limiting, such as epistaxis, ecchymosis, mucosal bleeding, menorrhagia, and hematuria, is classified as mild bleeding. Bleeding that requires hemodynamic support related to the upper and lower gastrointestinal (GI), respiratory, or urogenital systems but does not require a transfusion and is not associated with anemia is classified as moderate bleeding. Bleeding in critical regions or organs (e.g., intracranial, intraspinal, intraocular, retroperitoneal, pericardial bleeding) is classified as symptomatic major bleeding (5).

Specific antidotes, such as idarucizumab or andexanet alfa, or non-specific agents, such as prothrombin complex concentrate (PCC) or recombinant factor VIIa (rFVIIa), may be used to reverse anticoagulation in patients using DOACs (6). However, it is not always possible to obtain a supply of specific antidotes or rFVIIa. Therefore, emergency departments may use PCC in cases of life-threatening or moderate bleeding or when an urgent procedural intervention is required. This study aimed to evaluate the effectiveness and safety of PCC in patients using DOACs who presented either with major bleeding or required urgent procedural or surgical intervention necessitating reversal of anticoagulation in the emergency department.

Methods

Study Design

This retrospective review investigated the dosage and efficacy of PCC for the reversal of anticoagulation in patients admitted to the emergency department of a tertiary hospital between May 2022 and October 2024 for bleeding associated with DOAC use. Approval was obtained from the Local Ethics Committee of Recep Tayyip Erdoğan University before the study commenced (decision no: 2025/244, date: 02.06.2025). Furthermore, this study was conducted in accordance with the Declaration of Helsinki.

Study Population and Variables

Patients who fit the inclusion criteria were identified by searching the hospital information management system (HIMS). The inclusion criteria were (1) patients over 18 years of age who presented to the emergency department with an international normalized ratio (INR) value >1.5 and were using DOACs, and (2) patients who used DOACs and either experienced life-threatening intracranial, GI, or intra-abdominal bleeding, or required an urgent procedural or surgical intervention, even in the absence of active bleeding, for which pre-procedural reversal of anticoagulation was indicated. For the latter group, PCC was administered to lower the INR to <1.5, in accordance with perioperative anticoagulation recommendations stating that invasive procedures should ideally be performed when coagulation parameters are normalized or INR is below 1.5 (7). The exclusion criteria were (1) patients under 18 years of age; (2) patients with clinical symptoms or laboratory tests indicative of disseminated intravascular coagulation; (3) patients with a known congenital protein C, protein S, or antithrombin deficiency or a hereditary bleeding disorder; (4) patients with acute or chronic liver failure or renal failure or those on dialysis; and (5) patients who received fresh frozen plasma prior to PCC administration.

Data were obtained from HIMS and emergency department patient registration files. Specifically, data were collected

on demographic information (age, gender, comorbid diseases, drugs used to treat the diseases, the anticoagulant used, and the reason for its use), complaint at presentation, reason for the reversal of the anticoagulant effect, the coagulation parameters before and after treatment, the laboratory parameters for the renal and liver function test results, the treatment administered and the dose, the outcome in the emergency department, whether there was a need for inpatient follow-up and treatment, the number of days of follow-up, and the follow-up clinic.

Thromboembolic events were monitored throughout hospitalization and up to 30 days following PCC administration. Events were identified through clinical evaluation, laboratory findings (including elevated troponin or D-dimer values when available), and confirmatory imaging such as computed tomography (CT) angiography, brain CT/magnetic resonance imaging, or Doppler ultrasonography when clinically indicated. Documentation from outpatient follow-up visits and electronic hospital records was also reviewed to identify delayed thromboembolic events. Only clinically confirmed events were included in the analysis.

Treatment Protocols and Guidelines

The Turkish Medicines and Medical Devices Agency, which is affiliated with the Turkish Ministry of Health, defined the indications and dosing requirements for the use of four-factor PCC in patients with life-threatening bleeding to reverse anticoagulation (8). The dose is adjusted based on pretreatment INR, target INR, and body weight. In our study, patients received PCC or PCC plus vitamin K to reverse the anticoagulant effect. PCC use in the emergency department was based on weight, INR, and life-threatening conditions caused by coagulopathy.

Similarly, in a multicenter observational cohort by Singer et al. (9), which examined factor Xa inhibitor-associated intracranial and GI bleeding, a considerable proportion of patients presented with INR >1.5 or prolonged prothrombin time (PT) values and still received PCC for hemostatic reversal. This finding supports the clinical rationale for including patients with INR >1.5 and active bleeding or procedural indications in the current study population (9). In our institution, four-factor PCC is supplied and authorized under a national and local protocol that recommends its use in patients with coagulopathy and an INR value >1.5 in the setting of major bleeding or prior to urgent invasive procedures. Although INR is not a specific or sensitive measure of DOAC activity, this threshold is used as a pragmatic laboratory trigger to support clinical decision-making in the emergency department. Accordingly, in this retrospective study INR >1.5 was adopted as an inclusion criterion and as a marker of coagulopathy at presentation, in combination with a documented history of DOAC use and either active bleeding or the need for urgent procedural or surgical intervention.

Guidelines published by the European Society of Anaesthesiology and Intensive Care and the Thrombosis and Haemostasis Society of Australia and New Zealand offer recommendations for the management of patients presenting to an emergency department due to bleeding related to DOACs (6,10). The anticoagulant agent is temporarily discontinued, and then the patient's hemoglobin level is evaluated to determine the severity of the bleeding. Standard coagulation tests and liver and kidney function tests are ordered to determine the effect of the agent on the current clinical picture. General supportive care measures are provided to identify the source of the bleeding and limit ongoing bleeding. The use of PCC is considered in cases of major, life-threatening bleeding or for patients scheduled to undergo surgical procedures. If dabigatran is used as an oral anticoagulant, hemodialysis may be used as the last resort when idarucizumab is generally unavailable and PCC is ineffective.

Primary and Secondary Endpoints

The primary endpoint of this study was the change in coagulation parameters [PT, activated partial thromboplastin time (aPTT), and INR values] from baseline to within the first six hours after PCC administration. Secondary endpoints included all-cause in-hospital mortality, the occurrence of thromboembolic events within 30 days (including myocardial infarction, ischemic stroke, pulmonary embolism, or deep venous thrombosis), emergency department outcome (discharge, ward admission, or ICU admission), and total length of hospital stay. Additionally, changes in laboratory values at 48 hours after PCC administration were recorded to support treatment response assessment.

Statistical Analysis

All analyses were performed using Jamovi v.1.6 statistical software (The Jamovi Project, Sydney, Australia). Categorical data were expressed in frequency (n) and percentage. Normally distributed continuous variable data were described as mean plus standard deviation (SD), and non-normally distributed data as median and interquartile range (IQR). The normality of distribution was evaluated using the Shapiro-Wilk test. The t-test/paired t-test was applied in the comparison of continuous variables in the case of normal distribution, and the Mann-Whitney U/Wilcoxon test in the case of non-normal distribution. The chi-square test was used to compare categorical variables between the groups. In all statistical analyses, $p<0.05$ was considered significant.

Results

During the study period, 34 doses of four-factor PCC were administered to 20 patients. Regarding demographics, 65% of the patients were female, and the mean age was 81.00±14.30 (mean ± SD). The most commonly used anticoagulant agent was rivaroxaban (65%, n=13). In 75% of cases, an anticoagulant was used due to atrial fibrillation. The reason for presentation to the emergency

department was bruising in 25% of cases, confusion in 15%, and hematuria in 10%. In 35% of cases, after evaluation of patients, GI bleeding was the most common type of bleeding. A subset of patients (n=4; 20%) received PCC despite the absence of active bleeding because urgent procedural or surgical intervention was required. Therefore, these patients were not assigned a bleeding severity category and were instead classified separately as "no active bleeding (procedural indication)" Table 1 shows the demographic data of the patients. The most common risk factors increasing patients' susceptibility to bleeding due to DOAC use were renal dysfunction (40%, n=8), NSAID use (20%, n=4), aspirin (15%, n=3), and SSRI use (10%, n=2).

The median time to improvement in the coagulation parameters was 4.65 (IQR: 3.00-6.47) hours. There were statistically significant decreases in PT, aPTT, and INR immediately after treatment compared to pretreatment (p=0.001, p=0.003, p=0.001, respectively). Similarly, PT, aPTT, and INR were statistically lower 48 hours after treatment compared to pretreatment (p=0.001, p=0.001, p=0.001, respectively). However, when compared with the coagulation parameters 48 hours after treatment, only aPTT was significant (p=0.046). Table 2 shows the coagulation results before and after PCC administration. Regarding the dosages, 45% of the patients received 500 IU/20 mL PCC, 40% received 1000 IU/40 mL PCC, and 15% received 1500 IU/60 mL PCC.

Before treatment, 35% of the patients (n=7) had major bleeding in a critical body area, 20% (n=4) had moderate bleeding requiring hemodynamic support, and 25% (n=5) had mild bleeding. Of those with major bleeding, only one survived. When the emergency department outcomes of all patients were examined, after treatment, 25% (n=5) were discharged from the emergency department, 35% (n=7) were hospitalized in a clinic, and 40% (n=8) received follow-up care in the intensive care unit. Regarding hospital outcome, 50% (n=10) died. However, the relationship between treatment and hospital outcome was not statistically significant (p=0.42).

Four patients developed thromboembolic events after PCC administration. Two of these patients developed unstable angina pectoris with elevated cardiac markers after the administration of 500 IU/20 mL PCC. These two patients were discharged as outpatients after treatment. One of the other two patients developed acute ischemic stroke five days after the administration of 1000 IU/40 mL PCC, while the other patient developed pulmonary embolism 19 days after the administration of 1500 IU/60 mL PCC. Both patient's health outcome was death. Details are summarized in Table 3.

As part of the exploratory analyses, mortality-related clinical characteristics and laboratory results were compared between patients who survived and those who

Table 1. Demographic characteristics of the patients

Characteristics, n=20	Value
Age (years), mean ± SD	81.00±14.30
<65 years, n (%)	3 (15)
65-69 years, n (%)	0 (0)
70-74 years, n (%)	2 (10)
75-79 years, n (%)	2 (10)
>80 years, n (%)	13 (65)
Female gender, n (%)	13 (65)
Concomitant diseases	
Atrial fibrillation, n (%)	18 (90)
Hypertension, n (%)	15 (75)
Congestive heart failure, n (%)	9 (45)
Coronary artery disease, n (%)	8 (40)
Diabetes mellitus, n (%)	4 (20)
Chronic kidney disease, n (%)	4 (20)
Valvular heart disease, n (%)	3 (15)
Chronic obstructive pulmonary disease, n (%)	2 (10)
Cancer, n (%)	2 (10)
Presenting complaint	
Body bruises, n (%)	5 (25)
Shortness of breath, n (%)	4 (20)
Change in consciousness, n (%)	3 (15)
Urine with blood, n (%)	2 (10)
Bleeding from the anus, n (%)	2 (10)
Abdominal pain, n (%)	1 (5)
Vomiting with blood, n (%)	1 (5)
Deterioration in general condition, n (%)	1 (5)
Bloody stools, n (%)	1 (5)
Bleeding area	
Musculoskeletal system, n (%)	5 (25)
Gastrointestinal tract, n (%)	7 (35)
Urinary system, n (%)	2 (10)
Central nervous system, n (%)	2 (10)
No active bleeding (procedural indication), n (%)	4 (20)
Oral anticoagulant used	
Rivaroxaban, n (%)	13 (65)
Apixaban, n (%)	3 (15)
Edoxaban, n (%)	2 (10)
Dabigatran, n (%)	2 (10)
Reason for using anticoagulants	
Atrial fibrillation, n (%)	15 (75)
Valvular heart disease, n (%)	3 (15)
Pulmonary embolism, n (%)	2 (10)
Bleeding severity	
Major bleeding, n (%)	7 (35)
Moderate bleeding, n (%)	4 (20)
Mild bleeding, n (%)	5 (25)
No active bleeding, n (%)	4 (20)

Table 1. Continued

Characteristics, n=20	Value
Conditions that may pose a risk of bleeding	
Renal dysfunction, n (%)	8 (40)
Non-steroidal anti-inflammatory drug use, n (%)	4 (20)
Aspirin use, n (%)	3 (15)
SSRI use, n (%)	2 (10)
Steroid use, n (%)	1 (5)
Clopidogrel use, n (%)	1 (5)
Outcome in the emergency department	
Hospitalization in the intensive care unit, n (%)	8 (40)
Hospitalization, n (%)	7 (35)
Discharge from the emergency department, n (%)	5 (25)
Outcome after hospitalization	
Hospital discharge, n (%)	10 (50)
Death in hospital, n (%)	10 (50)
Length of hospitalization (days), median (IQR)	2.00 (0.75-7.50)

SD: Standard deviation, IQR: Interquartile range (25p, 75p), SSRI: Selective serotonin reuptake inhibitor

did not. The findings are summarized in Table 4. Patients in the mortality group more frequently presented with major bleeding compared with the non-mortality group (p=0.036). However, there were no statistically significant differences between groups regarding age, sex, DOAC type, baseline coagulation parameters (PT, aPTT, INR), or oral anticoagulant agent used. These subgroup comparisons were exploratory and interpreted with caution due to the small sample size.

Discussion

In line with international guideline recommendations, the present study found that four-factor PCC was effective in reversing the effects of DOACs and maintaining hemostasis. However, the relationship between the mortality rates of the patients and the treatment protocol applied was not found to be significant. These findings are similar to those of previous studies (11,12).

Although the use of specific antidotes, such as andexanet alfa or idarucizumab, is a priority in patients who experience major bleeding after DOAC use, it may not always be possible to obtain specific antidotes. In such cases, the use of PCC, a non-specific hemostatic agent, is recommended (10). This study investigated cases in which four-factor PCC was used because specific antidotes were not available. Improvement in coagulation parameters was detected at 4.65 hours, which is the median improvement value after treatment. This improvement period in coagulation parameters is especially important in the management of patients presenting with major life-threatening bleeding and in cases where urgent interventional procedures are planned. Additionally, in accordance with the predefined primary endpoint, PCC administration resulted in a statistically significant improvement in coagulation parameters shortly after treatment. This finding supports existing evidence indicating that PCC can provide rapid reversal of DOAC-related coagulopathy, particularly in settings where specific antidotes are not available.

Hemoglobin is the main tool used to evaluate the severity of bleeding due to DOAC use. However, standard coagulation tests (thrombin time, PT, aPTT) should be evaluated to determine the degree to which the drug contributes to bleeding in emergency conditions and the need for intervention (10). In this study, the improvements in the coagulation parameters before and right after treatment and in the coagulation parameters measured 48 hours after treatment were statistically significant. However, the INR used for warfarin was not statistically significant 48

Table 2. Statistics of laboratory parameters

Laboratory parameters	Pre-treatment	Post-treatment	p-value*	Pre-treatment	48th hour	p-value*	Post-treatment	48th hour	p-value*
PT (sec.), median (IQR)	91.20 (44.70-120.00)	32.00 (23.60-62.00	**0.001**	91.20 (44.70-120.00)	21.10 (9.80-37.10)	**0.001**	32.00 (23.60-62.00)	21.10 (9.80-37.10)	0.121
aPTT (sec.), median (IQR)	54.70 (44.40-76.00)	42.60 (34.00-56.10)	**0.003**	54.70 (44.40-76.00)	32.90 (19.60-51.70)	**0.001**	42.60 (34.00-56.10)	32.90 (19.60-51.70)	**0.046**
INR, median (IQR)	7.28 (3.67-10.60)	2.73 (1.94-4.96)	**0.001**	7.28 (3.67-10.60)	1.61 (0.78-3.00)	**0.001**	2.73 (1.94-4.96)	1.61 (0.78-3.00)	0.142

*: Wilcoxon test, IQR: Interquartile range (25p, 75p), PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

Table 3. Characteristics of thromboembolic events

Type of event	Timing after PCC	PCC dose	DOAC used	Outcome
Unstable angina	<24 hours	500 IU	Rivaroxaban	Survived
Unstable angina	<24 hours	500 IU	Apixaban	Survived
Ischemic stroke	Day 5	1000 IU	Rivaroxaban	Death
Pulmonary embolism	Day 19	1500 IU	Dabigatran	Death

PCC: Prothrombin complex concentrate, DOAC: Direct oral anticoagulant, IU: International unit

Table 4. Statistical analysis between mortality and non-mortality groups

Characteristics, n=20	Mortality groups, n=10	Non-mortality groups, n=10	p-value
Age (years), mean ± SD	85.1±8.03	76.8±18.2	0.203*
Gender			
Male	4	3	0.639^
Female	6	7	
Bleeding severity			
Major bleeding	6	1	
Moderate bleeding	2	2	**0.036^**
Mild bleeding	0	5	
None	2	2	
Oral anticoagulant used			
Rivaroxaban	6	7	
Apixaban	2	1	0.220^
Edoxaban	2	0	
Dabigatran	0	2	
First presenting PT (sec.), median (IQR)	103 (IQR: 72.7-120)	49.3 (IQR: 40.1-121)	0.623#
First presenting aPTT (sec.), median (IQR)	58.1 (IQR: 47.4-63.6)	49.9 (IQR: 36.7-83.9)	0.436#
First presenting INR, median (IQR)	8.71 (IQR: 5.94-11.5)	3.98 (IQR: 3.38-10.1)	0.427#

*: Student-t test, ^: Chi-square test, #: Mann-Whitney U test, SD: Standard deviation, IQR: Interquartile range (25p, 75p), PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International normalized ratio

hours after treatment. In this study, 40% of the patients had renal dysfunction, which increased their susceptibility to bleeding. Therefore, our recommendation for future studies is that creatinine should also be measured to assess renal function and estimate the expected rate of anticoagulant drug clearance.

Bleeding is a risk with all anticoagulant therapies. However, this risk is lower with DOACs than with traditional vitamin K antagonists, such as warfarin (13). Nevertheless, caution should be exercised with respect to modifiable individual risk factors, such as hypertension, antiplatelet therapy, NSAID use, and SSRI use, which may increase susceptibility to bleeding. In this study, 75% of the patients had hypertension as a comorbidity, and 20% had a history of NSAID use, which increased their predisposition to bleeding. Meanwhile, five of the seven patients in the major bleeding group had a history of clopidogrel and/or SSRI and/or aspirin use. Patients with a history of DOAC use should be warned about drug interactions. Meanwhile, age was a non-modifiable risk factor. In this study, 65% of the patients were 80 years of age or older, and the mean age was 81.00±14.30 years, increasing the risk of bleeding. These findings underline that the clinical burden and safety concerns of PCC administration are particularly relevant to geriatric emergency medicine, where age-related vulnerability and polypharmacy are common.

To manage bleeding, it is important to determine the severity and extent of the bleeding. A patient's current clinical status guides the initial evaluation. In this study, 25% of the patients presented to the emergency department with bruising and complaints of GI tract bleeding. This rate is similar to the rates reported in previous studies (14,15). Regarding the severity of the bleeding, major bleeding ranked first, affecting 35% of the patients, and only one of these patients was discharged from the hospital. The mortality rate for all patients included in the study was 50%, which is higher than in another study (16). The relationship between health outcome and the treatment protocols applied was not significant. This high mortality rate may be attributed to the advanced age and comorbidities of the study population, the predominance of major bleeding cases involving critical organs, and delayed presentation to the emergency department. Additionally, the limited availability of specific antidotes and the retrospective nature of data collection may have influenced treatment optimization and outcomes.

Bleeding that occurs as a complication of anticoagulant treatment may lead to thromboembolic complications (TEC) after PCC is administered and the anticoagulant treatment is discontinued (17). In this study, TEC developed in four patients, and death occurred in two of four patients who received more than one dose of PCC. However, it could not be determined whether this complication was related to the PCC dosage or the discontinuation of the anticoagulant treatment.

Additionally, exploratory subgroup comparisons did not reveal statistically significant differences between survival status and baseline laboratory parameters or DOAC type; however, patients with major bleeding were more frequently represented in the mortality group,

consistent with the known severity-outcome relationship in anticoagulated emergency populations.

While the study is limited by scale and design, it reflects a real-world treatment landscape in which DOAC-treated patients are often elderly, frail, and medically complex, and where PCC may be used in the absence of specific reversal agents. This context contributes clinically relevant insight into emergency management patterns in resource-constrained settings and may help inform future prospective studies.

Study Limitations

This study has several limitations. As a retrospective study, it was limited by the documentation and accessibility of the information in the patients' medical records. Details about a patient's medical history and notes written by attending physicians in emergency department patient files are not always easily accessible. In addition, the relationship between treatment and mortality could not be determined due to the limited patient cohort design. Furthermore, it could not be determined whether the TECs that occurred were due to the PCC administration or the discontinuation of the anticoagulant therapy. Another limitation is that thromboembolic events were captured only when clinically recognized or documented within the available hospital and follow-up records; therefore, asymptomatic or post-discharge events without medical contact may have been missed. This may result in underestimation of the true incidence of TECs. During case selection, an INR >1.5 was chosen as the inclusion threshold in accordance with the institutional PCC administration protocol; however, coagulation parameters affected by the anticoagulant, such as aPTT and PT, were not specifically evaluated for each agent. An important limitation of this study is the use of INR >1.5 as both a trigger for PCC administration and an inclusion criterion in DOAC-treated patients. INR is known to be an unreliable surrogate of DOAC activity; a normal INR does not exclude clinically relevant anti-Xa or anti-IIa effects, while modest INR prolongation may be influenced by liver dysfunction, concomitant medications, or laboratory variability rather than by the DOAC itself. Consequently, INR in this cohort should be interpreted as a pragmatic marker of global coagulopathy within our institutional protocol, rather than as a precise measure of DOAC intensity. This limitation may have introduced heterogeneity in the baseline degree of anticoagulation and restricts the extent to which the observed changes in INR can be directly equated with reversal of DOAC effect. Our findings should therefore be understood as reflecting real-world PCC use in an emergency setting guided by an INR-based protocol, rather than as a mechanistic evaluation of DOAC reversal. Moreover, information regarding the timing of the last DOAC dose, renal function (estimated glomerular filtration rate), and drug-specific subgroup analyses (rivaroxaban, apixaban, dabigatran) was incomplete, which may have influenced the assessment of pharmacokinetic variability and treatment response.

Conclusion

The present study's findings showed that four-factor PCC led to a rapid and statistically significant improvement in coagulation parameters in DOAC-treated patients, both in those presenting with major bleeding and in those requiring urgent procedural intervention. However, PCC's effect on the mortality rate was not fully determined. Meanwhile, it was found that PCC might increase the risk of thromboembolism. Although PCC is an important option when specific antidotes are unavailable, the risk of complications should be considered.

Ethics

Ethics Committee Approval: Approval was obtained from the Local Ethics Committee of Recep Tayyip Erdoğan University before the study commenced (decision no: 2025/244, date: 02.06.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.G., Ö.B., Concept: G.E., İ.A., Design: İ.A., M.M.Y., Ö.B., Data Collection or Processing: G.E., M.M.Y., Analysis or Interpretation: G.E., M.M.Y., E.G., Ö.B., Literature Search: İ.A., Ö.B., Writing: G.E., İ.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Steiner T, Böhm M, Dichgans M, Diener HC, Ell C, Endres M, et al. Recommendations for the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. Clin Res Cardiol. 2013;102:399-412.
2. Grottke O, Aisenberg J, Bernstein R, Goldstein P, Huisman MV, Jamieson DG, et al. Efficacy of prothrombin complex concentrates for the emergency reversal of dabigatran-induced anticoagulation. Crit Care. 2016;20:115.
3. Adam SS, McDuffie JR, Ortel TL, Williams JW Jr. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med. 2012;157:796-807.
4. White K, Faruqi U, Cohen AAT. New agents for DOAC reversal: a practical management review. Br J Cardiol. 2022;29:1.
5. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3:692-4.
6. Grottke O, Afshari A, Ahmed A, Arnaoutoglou E, Bolliger D, Fenger-Eriksen C, et al. Clinical guideline on reversal of direct oral anticoagulants in patients with life threatening bleeding. Eur J Anaesthesiol. 2024;41:327-50.

7. Douketis JD, Spyropoulos AC, Murad MH, Arcelus JI, Dager WE, Dunn AS, et al. Perioperative management of antithrombotic therapy: an American College of Chest Physicians Clinical Practice guideline. Chest. 2022;162:e207-43.
8. Turkish Medicines and Medical Devices Agency. Cofact 500 IU/20 mL product information [Internet]. 2019 (cited 2025 Nov 10). Available from: URL: https://pdf.ilacprospektusu.com/30206-cofact-500-iu-20-ml-iv-enjeksiyon-icin-toz-iceren-flakon-kt.pdf
9. Singer AJ, Concha M, Williams J, Brown CS, Fernandes R, Thode HC Jr, et al. Treatment of factor-Xa inhibitor-associated bleeding with andexanet alfa or 4 factor PCC: a multicenter feasibility retrospective study. West J Emerg Med. 2023;24:939-49.
10. Tran HA, Merriman E, Baker R, Curnow J, Young L, Tan CW, et al. 2025 Guidelines for direct oral anticoagulants: a practical guidance on the prescription, laboratory testing, peri-operative and bleeding management. Intern Med J. 2025;55:1174-83.
11. Wallwork S, Wang Y, Chaiwatanatorn K, Cole-Sinclair M. Prothrombin complex concentrates for the urgent reversal of apixaban and rivaroxaban: an Australian retrospective cohort study. Intern Med J. 2023;53:803-11.
12. Schultz NH, Tran HTT, Bjørnsen S, Henriksson CE, Sandset PM, Holme PA. The reversal effect of prothrombin complex concentrate (PCC), activated PCC and recombinant activated factor VII against anticoagulation of Xa inhibitor. Thromb J. 2017;15:6.
13. Niessner A, Tamargo J, Morais J, Koller L, Wassmann S, Husted SE, et al. Reversal strategies for non-vitamin K antagonist oral anticoagulants: a critical appraisal of available evidence and recommendations for clinical management-a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis. Eur Heart J. 2017;38:1710-6.
14. Green L, Tan J, Antoniou S, Alikhan R, Curry N, Everington T, et al. Haematological management of major bleeding associated with direct oral anticoagulants - UK experience. Br J Haematol. 2019;185:514-22.
15. Giugliano RP, Ruff CT, Wiviott SD, Nordio F, Murphy SA, Kappelhof JA, et al. Mortality in patients with atrial fibrillation randomized to edoxaban or warfarin: insights from the ENGAGE AF-TIMI 48 trial. Am J Med. 2016;129:850-7.e2.
16. 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;13:2012-20.
17. Milling TJ Jr, Refaai MA, Goldstein JN, Schneider A, Omert L, Harman A, et al. Thromboembolic events after vitamin K antagonist reversal with 4-factor prothrombin complex concentrate: exploratory analyses of two randomized, plasma-controlled studies. Ann Emerg Med. 2016;67:96-105.e5.