MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Reversal of Apixaban and Rivaroxaban: Evidence for Fixed-Dose vs Weight-Based Dose of Prothrombin Complex Concentrate

by Anastasia E. Boutris, 2026 PharmD Candidate, Christina D. Choi, 2026 PharmD Candidate, Maura C. Keenan, 2026 PharmD Candidate

Abstract

Reversing anticoagulation in emergency situations is crucial but challenging, as it requires selecting the correct agent and dosage based on the specific circumstances. Direct factor Xa inhibitors, such as rivaroxaban and apixaban, require either andexanet alfa or prothrombin complex concentrate (PCC) for reversal. For PCC administration, evidence supports both fixed dosing and weight-based dosing. This literature review's findings suggest that a fixed dosing of PCC is non-inferior to the weight-based dose. Furthermore, utilizing a fixed dose may improve patient outcomes, enhance safety, and streamline administration.

Direct factor Xa inhibitors, such as rivaroxaban and apixaban, are anticoagulants that selectively and reversibly bind to the active site of factor Xa, an essential enzyme in the coagulation process that is responsible for converting prothrombin to thrombin. In the clotting cascade, the extrinsic and intrinsic pathways converge at factor Xa activation, which subsequently activates prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, leading to clot formation, as depicted in Figure 1. By inhibiting factor Xa, medications like rivaroxaban and apixaban reduce thrombin generation and prevent clot formation. Direct factor Xa inhibitors offer several advantages over other oral anticoagulants, such as warfarin, including; similar or improved outcomes related to thrombosis, predictable pharmacokinetics and pharmacodynamics, fixed dosing without routine monitoring, and a favorable safety profile with lower risk for major bleeding.[1]

Indications for direct factor Xa inhibitors include stroke prevention in atrial fibrillation, treatment and prevention of venous thromboembolism, and management of coronary artery disease. Rivaroxaban also has peripheral artery disease as an indication. Between rivaroxaban and apixaban, although efficacy is similar, apixaban may be preferred due to its lower risk of major bleeding and its superior safety profile in elderly patients and those with impaired kidney function. However, there are also advantages to rivaroxaban, such as its once-daily dosing. Additionally, studies have demonstrated that rivaroxaban exhibits favorable kinetics in obese patients when compared to apixaban, with similar peak plasma concentrations, distribution, and half-life in obese patients to those seen in patients of normal weight.[1-4]

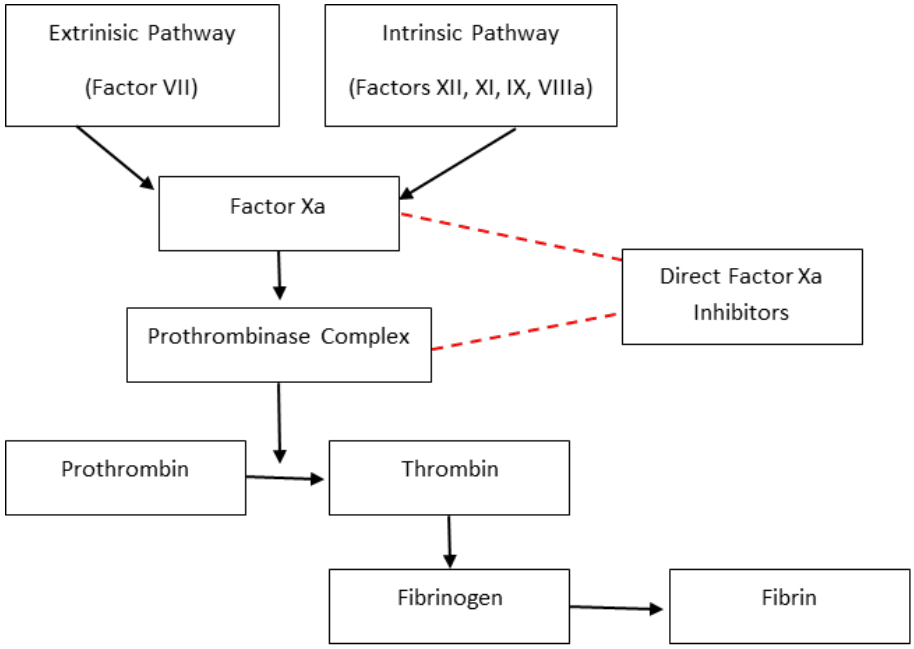
Despite their benefits related to decreased risk of thrombosis, direct factor Xa inhibitors are not without risks. Common side effects include easy bruising, weakness, dizziness, anemia, and alterations in liver function tests. More serious complications, such as major bleeding events, may occur and necessitate the use of specialized reversal agents to manage effectively.[2,3]

Prothrombin complex concentrates (PCCs) are commonly used to reverse anticoagulation, particularly in bleeding events associated with vitamin K antagonists (VKAs).[5] PCCs function by quickly raising blood levels of vitamin K-dependent coagulation factors, primarily factors II, VII, IX, and X.[6] Factor VII starts the extrinsic pathway, while factors IX and X contribute in the intrinsic and common pathways; these ultimately result in the formation of fibrin and thrombin, essential factors in the coagulation cascade. For direct oral anticoagulants (DOACs) like apixaban and rivaroxaban, specific reversal agents are preferred when accessible. Andexanet alfa is Food and Drug Administration (FDA) approved and recommended for reversing apixaban and rivaroxaban according to the 2020 American College of Cardiology (ACC) Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants.[5] However, in the absence of specific agents, PCCs are often used off-label for DOAC reversal, with four-factor PCCs (4F-PCCs) generally favored over three-factor PCCs (3F-PCCs) due to their greater efficacy in reversing anticoagulation. Factors II, IX, and X are present in 3F-PCCs, but factor VII is present only in small quantities.[7] Factor II, VII, IX, and X are present in 4F-PCCs, along with greater amounts of factor VII than in 3F-PCCs. Comparisons of the relative safety and effectiveness of 3F-PCCs and 4F-PCCs are not well documented. Studies indicate that use of 4F-PCCs shows comparable effectiveness in mortality when compared to andexanet alfa in reversing factor Xa inhibitors. The choice between PCCs and specific reversal agents is often

influenced by factors such as availability, cost, and clinical context.[5]

While several guidelines propose 4F-PCC as a suitable option for factor Xa inhibitor reversal, dosing recommendations differ widely.[5,8] Some suggest a fixed dose of 2,000 units for major bleeding, while others advocate for weight-based dosing ranging from 25 to 50 units/kg. Ultimately, the ideal dosing strategy for 4F-PCC in managing major bleeding associated with factor Xa inhibitor reversal remains uncertain. Currently, dosing recommendations vary slightly in the literature; however, general recommendations are 2,000 units IV once or 25-50 units/kg once.[5,9] While the ACC guidelines on management of bleeding in patients on oral anticoagulants do not currently define whether weight-based or fixed-based dosing is superior, studies suggest that there may be a difference in efficacy and outcomes pertaining to mortality or thrombolytic events.[5,8] This narrative review will describe the evidence exploring the efficacy and safety of weight-based versus fixed-based dosing.

FIGURE 1. The Coagulation Cascade Highlighting the Site of Action of Direct Factor Xa Inhibitors



Evidence Supporting Weight-Based Dosing of PCC

Weight-based dosing of 4F-PCC has been shown to be an effective and safe strategy for reversing major bleeding associated with apixaban and rivaroxaban use. A retrospective cohort analysis conducted by Tao et al. evaluated the safety profile of 4F-PCC in patients (n=43) requiring emergent reversal of anticoagulation, dosed at 25-50 units/kg, due to major bleeding events associated with factor Xa inhibitors. The results demonstrated that 4F-PCC was effective in achieving hemostasis in a significant proportion of patients, with a low incidence of thromboembolic events.[10]

A study by Davis et al., published in 2021 in *The Journal of Thrombosis Research*, compared high-dose (≥35 units/kg) versus low-dose (<35 units/kg) 4F-PCC for factor Xa inhibitor reversal in patients (n=89) with intracranial hemorrhage (ICH) who had been taking apixaban, rivaroxaban, or edoxaban. The study found hemostasis was achieved in 82% of all patients. The high-dose group had significantly higher hemostasis achievement (89.2% vs. 46.7%; OR 11.2; 95% CI 2.4-52.6, p = 0.002) without a significant increase in thrombotic events, aligning with guidelines available at that time. Overall, the authors concluded that a high-dose weight-based 4F-PCC strategy has greater efficacy than a low-dose weight-based strategy. They also suggest that a high-dose strategy may be superior to fixed dosing if the fixed dose results in a low weight-based dose (<35 units/kg).[11]

Similarly, a study by Castillo et al., published in 2021 in *The Journal of Thrombosis and Thrombolysis*, also evaluated the efficacy of weight-based dosing of 4F-PCC compared to activated prothrombin complex concentrates (aPCC) in patients with intracranial hemorrhage (ICH) associated with the use of rivaroxaban or apixaban. Here, they found success in achieving hemostasis with both high (≥30 units/kg) and low (<30 units/kg) 4F-PCC doses in 89% of patients, with no significant differences between the dosing groups.[12]

Additionally, a study by Highsmith et al., published in 2021 in *The Journal of Clinical Pharmacology*, performed a retrospective review of patient electronic health records (EHRs) to assess the effectiveness of 4F-PCC in reversing the effects of oral factor Xa inhibitors in 38 patients with bleeding. The median dose of 4F-PCC used in the study sample was 50 units/kg. The study found that 74% of patients achieved hemostasis. Notably, patients who achieved hemostasis had a median dose of 50 units/kg, whereas those who did not achieve hemostasis had a median dose of 30 units/kg. The study also conducted a subgroup analysis, comparing 4F-PCC with andexanet alfa, which showed no significant difference in overall rates of hemostasis between the two groups, supporting the use of 4F-PCC as an effective alternative.[13]

Overall, there is clear evidence for efficacy in using weight-based dosing with 4F-PCC. Both the 2017 and 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants state that dosing 4F-PCC at 50 units/kg is a reasonable option for emergency reversal of factor Xa inhibitors like rivaroxaban and apixaban in the setting of major bleeding events.[5,8] There is also emerging evidence suggesting that fixed dosing of 4F-PCC may be superior, necessitating additional analyses comparing the two strategies.

Evidence Supporting Fixed-Dose PCC

Guidance for the reversal of direct oral anticoagulants from the Anticoagulation Forum published in March 2019 states that patients with rivaroxaban- and apixaban-associated major bleeding, if

andexanet alfa is not available, should be treated with 4F-PCC 2,000 units.[9] This recommendation was derived from two studies showing a 65-69% effectiveness in achieving hemostasis. The first study looked at a total of 84 patients in which a 2,000-unit dose of 4F-PCC had an effective rate of 69% for patients who had a major bleeding event. In traumatic vs. nontraumatic bleeding patients, there was no difference in efficacy (73.1% traumatic bleeding, 67.2% non-traumatic) (p=0.8).[14] In the other study, 66 patients were included who had received a fixed dose of 2,000 units of PCC to measure hemostasis, rated on a scale of good, moderate, and poor utilizing an assessment guide. The assessment guide classified "good" as cessation of bleeding within 1 hour and no additional coagulation intervention needed. "Moderate" indicated that it took between 1 and 4 hours to control the bleeding, while "poor" indicated more than 4 hours to control the bleeding or additional intervention required. Results ranged for good with 43 patients (65%; 95% CI 53–77), moderate with 13 (20%; 95% CI 10–30), and poor/none with 10 patients (15%; 95% CI 6–24). It was also noted that there was no difference between apixaban and rivaroxaban patients.[15] Overall, based on these two studies, it was concluded that if andexanet alfa is not available, it is safe and effective to initiate 2,000 unites of 4F-PCC to reverse the anticoagulation from apixaban and rivaroxaban.

Comparison of Weight-Based vs Fixed-Dose PCC

A meta-analysis published by Chaisakul et al. in 2023 in *Research and Practice in Thrombosis and Haemostasis*, supports the use of fixed dosing as a safe and effective alternative to weight-based dosing for reversal of factor Xa inhibitors. This meta-analysis included 25 studies with a total of 1,760 patients (fixed dosing n= 228 and weight-based dosing n= 1,532). For hemostatic effectiveness, weight-based dosing had a 79.2% effectiveness (95% CI 74.4-83.7), while fixed dosing had 74.2% (95% CI 52.3-91.3, p = 0.65). In terms of thromboembolic events, weight-based dosing had a 4.1% rate of events (95% CI 2.2-6.3) compared to fixed dosing which had 2.9% (95% CI 0.0-8.7, p = 0.48). Lastly, the all-cause mortality rate with weight-based dosing was 21.4% (95% CI 16.4-26.8), while fixed dosing had 15.9% (95% CI 10.4-22.3, p=0.14). One important note was that the hospital stay was significant longer in the fixed group with 7.4 days (95% CI 3.6-11.1) compared to the weight-based dose at 5.9 days (95% CI 5.5-6.3) (p<0.001).[16]

Additionally, a systematic review and meta-analysis by Alwakeal et al., published in *Critical Care Medicine* in 2024, explored the published evidence comparing the safety and effectiveness of a fixed-dose regimen of 4F-PCC with a manufacturer-recommended, weight-based-dose regimen. Three randomized trials totaling 323 participants (161 in fixed dosage and 162 in weight-based dosage) and sixteen cohort studies totaling 1,912 patients (858 in fixed-dose and 1,054 in weight-based dose) made up the analysis. Compared to a weight-based-dose regimen, a fixed-dose regimen might result in a lower 4F-PCC dose (95% CI, –1.3 to –0.8; low certainty), as well as a significant reduction in the order-to-needle time (95% CI, –0.6 to –0.2; high certainty). A fixed-dose regimen also demonstrated an increased likelihood of clinical hemostasis, as well as a decrease in both mortality and thromboembolic events.[17] Table 1 summarizes the evidence for fixed and weight-based dosing of PCC in reversal of factor Xa inhibitors.

Clinical Implications

The 2020 ACC Expert Consensus on the Management of Bleeding currently recommends using andexanet alfa as a first line therapy, and if it is not available, it is reasonable to use a dose of 50 units/kg of aPCC or 4F-PCC, or 2,000 units of 4F-PCC.[5] There is not a clear and strong recommendation for either fixed or weight-based dosing, with evidence supporting either strategy as viable. There is a non-significant trend suggesting that fixed dosing may result in higher rates of hemostasis, but with a low degree of certainty. The additional benefits of a fixed-dose regimen based on available evidence appear to be a trend toward lower mortality and thromboembolic events, shorter administration times, and reduced dose and cost of 4F-PCC per patient. Health systems need to evaluate the data and work with stakeholders to decide on a consistent approach to anticoagulant reversal. This review should outline medication and dosing for reversal of anticoagulants that account for local data, ongoing success, and preferences.

There is consensus among the subject matter experts that there is a need for additional research to investigate whether either dosing strategy is superior.[5,8] Ideally, these future studies should aim to address gaps by including diverse patient populations. Additionally, more cost-benefit analyses comparing both strategies in different healthcare and geographical settings could provide further insights into optimal PCC dosing practices. A study done in the Netherlands demonstrated that a low fixed-dose strategy resulted in savings of approximately €1,634–€2,100 per patient compared to weight-based dosing for vitamin K antagonist-associated bleeding emergencies. Therefore, fixed dosing may decrease costs but should be further analyzed.[18] These analyses should account for direct and indirect costs, such as the drug itself, preparation times, staff training, and potential delays in care. In general, these future findings could guide pharmacists and health systems in shaping guidelines that prioritize both patient outcomes and resource efficiency.

Conclusion

The evidence presented demonstrates that both weight-based and fixed dosing strategies for PCC are safe and effective. With weight-based dosing, current guidelines recommend using a dose of 50 units/kg for emergency situations. However, there is growing interest in fixed dosing strategies, with evidence supporting 2,000 units administered once is non-inferior to weight-based dosing and may offer advantages such as simpler administration and reduced overall usage without compromising efficacy or safety. While current evidence supports the use of both strategies, ongoing research is needed to explore their applications across diverse patient populations and clinical scenarios.

TABLE 1. Selected Studies Reporting Outcomes of Anticoagulation Reversal of Direct Factor Xa Inhibitors with Different Dosing Strategies of 4-Factor Prothrombin Complex Concentrates (4F-PCC)

Study	*Study Design*	*Number of Patients*	*Type(s) of Bleed*	*Dosing Strategy*	*Outcomes*
Tao et al.[10]	Retrospective review of patients who received 4F-PCC	43	• Gastrointestinal bleed • Intracranial hemorrhage – traumatic and non-traumatic • Trauma • Other	• 25 units/kg (n=22) • 25-50 units/kg (n=4) • 50 units/kg (n=16) • >50 units/kg (n=1)	• Based on data, dose of 25-50 IU/kg in emergent reversal of factor Xa inhibitors is acceptable. • Only 3 of 43 patients continued to have active bleeding after 4F-PCC. • Thromboembolic events within 14 days of receiving 4F-PCC occurred in 1 of 43 patients.
Davis et al.[11]	Multi-center, retrospective, cohort study of patients with intracranial hemorrhage who received 4F-PCC	89	Intracranial hemorrhage	• High dose: ≥35 units/kg (n=74) • Low dose: <35 units/kg (n=15)	• Hemostasis was achieved in 82% of all patients. • Hemostasis achievement was statistically higher in high dose compared to low dose (89.2% vs 46.7%; OR 11.2; 95% CI 2.4–52.6, P = 0.002). • The high dose strategy has greater efficacy and may been superior than fixed dosing if fixed dosing results in low weight-based dosing (<35 units/kg).
Castillo et al.[12]	Multi-center, retrospective study of patients with intracranial hemorrhage who received aPCC or 4F-PCC *Analysis focused on 4F-PCC patients	37 4F-PCC patients	Intracranial hemorrhage (intraparenchymal hematoma, subarachnoid bleed, subdural hematoma)	• High dose: ≥30 units/kg (n=19) • Low dose: <30 units/kg n=18)	• Hemostatic efficacy was well achieved in both high and low dose 4F-PCC. • No significant differences were seen between the two groups.
Highsmith et al.[13]	Retrospective, descriptive study analyzing electronic health records for 4F-PCC administration and factor Xa inhibitors	38	• Intracranial hemorrhage • Gastrointestinal bleed • Other	• Median dose = 50 units/kg • IQR = 25-50 units/kg	• 74% of patients achieved hemostasis. • Of the 38 patients, 28 achieved hemostasis with a median dose of 50 units/kg. • 10 patients did not achieve hemostasis and had a media dose of 30 units/kg.
Majeed et al. [14]	Prospective observational study	84	• Intracranial hemorrhage • Gastrointestinal bleed • Traumatic bleed	Median dose = 2,000 units	69.1% of patients achieved hemostasis
Schulman et al. [15]	Prospective cohort study	66	• Intracranial hemorrhage • Gastrointestinal bleed	• Fixed dose of 1,000 units for non-intracranial bleeding • Fixed dose of 1500 units for intracranial hemorrhage	80.6% of patients achieved hemostasis
Chaisakul et al.[16]	Meta analysis of 25 total studies	• Fixed dosing N=228 • Weight-based N=1,532	Various	• Fixed ranged between 1,500-2,000 units • Weight-based ranged between 25 units/kg-50 units/kg	• Fixed dosing had a less thromboembolic events 2.9% vs 4.1% (p=0.48) and less all cause mortality 15.9% vs 21.4% (p=0.14). • Weight-based dosing had shorter hospital stays 5.9 days vs 7.4 days (p<0.001).
Alwakeal et al.[17]	Systematic review and meta-analysis of 3 randomized trials and 16 cohort studies	• 323 from randomized trials • Fixed dosing N=161 • Weight-based N= 162 • 1912 from cohort studies • Fixed dosing N= 858 • Weight-based N= 1054	• Extracranial bleeding • Intracranial hemorrhage	• Fixed dose ranged between 1,000-2,000 units • Weight- based dose ranged between 15 units/kg- 25 units/kg	Fixed-dose regimen might result in a lower 4F-PCC dose (95% CI, –1.3 to –0.8; low certainty), as well as a significant reduction in the order-to-needle time (95% CI, –0.6 to –0.2; high certainty)

aPCC: activated prothrombin complex concentrates, IQR: interquartile range

Anastasia Boutris is a 2026 Doctor of Pharmacy Candidate at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Christina Choi is a 2026 Doctor of Pharmacy Candidate at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI. Maura Keenan is a 2026 Doctor of Pharmacy Candidate at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Corresponding Author:
Maura Keenan - mkeenan@mcw.edu

Disclosure: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

References

1. Kustos SA, Fasinu PS. Direct-acting oral anticoagulants and their reversal agents-an update. *Medicines (Basel)*. 2019;6(4):103. doi:10.3390/medicines6040103
2. Rivaroxaban. In: Lexi-Drugs. UpToDate Inc; 2024. Updated November 29, 2024. Accessed November 29, 2024. https://online.lexi.com
3. Apixaban. In: Lexi-Drugs. UpToDate Inc; 2024. Updated November 28, 2024. Accessed November 29, 2024. https://online.lexi.com
4. Martin KA, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemost*. 2021;19(8):1874-1882. doi:10.1111/jth.15358
5. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: A report of the American College of Cardiology Solution Set Oversight Committee [published correction appears in *J Am Coll Cardiol*. 2021 Jun 1;77(21):2760. doi: 10.1016/j.jacc.2021.04.020]. *J Am Coll Cardiol*. 2020;76(5):594-622. doi:10.1016/j.jacc.2020.04.053
6. Franchini M, Lippi G. Prothrombin complex concentrates: an update. *Blood Transfus*. 2010;8(3):149-154. doi:10.2450/2010.0149-09
7. Mora L, Maegele M, Grottke O, et al. Four-factor Prothrombin Complex Concentrate use for bleeding management in adult trauma. *Anesthesiology*. October 30, 2024. doi:10.1097/ALN.0000000000005230
8. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: A report of the American College of Cardiology Task Force on expert consensus decision pathways. *J Am Coll Cardiol*. 2017;70(24):3042-3067. doi:10.1016/j.jacc.2017.09.1085
9. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the Anticoagulation Forum. *Am J Hematol*. 2019;94(6):697-709. doi:10.1002/ajh.25475
10. Tao J, Bukanova EN, Akhtar S. Safety of 4-factor prothrombin complex concentrate (4F-PCC) for emergent reversal of factor Xa inhibitors. *J Intensive Care*. 2018;6:34. doi:10.1186/s40560-018-0303-y
11. Davis SD, Chauv S, Hickman AW, Collingridge DS, Kjerengtroen S, Fontaine GV. High-dose versus low-dose 4-factor prothrombin complex concentrate for factor Xa inhibitor reversal in intracranial hemorrhage. *Thromb Res*. 2021;208:112-116. doi:10.1016/j.thromres.2021.10.026
12. Castillo R, Chan A, Atallah S, et al. Treatment of adults with intracranial hemorrhage on apixaban or rivaroxaban with prothrombin complex concentrate products [published correction appears in *J Thromb Thrombolysis*. 2021 Jan;51(1):246. doi: 10.1007/s11239-020-02197-2.
13. Highsmith EA, Morton C, Varnado S, Donahue KR, Sulhan S, Lista A. Outcomes associated with 4-factor prothrombin complex concentrate administration to reverse oral factor Xa inhibitors in bleeding patients. *J Clin Pharmacol*. 2021;61(5):598-605. doi:10.1002/jcph.1779
14. Majeed A, Ågren A, Holmström M, et al. Management of rivaroxaban-or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017;130:1706-1712.
15. Schulman S, Gross PL, Ritchie B, et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost*. 2018;118:842-851.
16. Chiasakul T, Crowther M, Cuker A. Four-factor prothrombin complex concentrate for the treatment of oral factor Xa inhibitor-associated bleeding: a meta-analysis of fixed versus variable dosing. *Res Pract Thromb Haemost*. 2023;7(2):100107. doi:10.1016/j.rpth.2023.100107
17. Alwakeal A, Maas MB, Naidech AM, Jahromi BS, Potts MB. Fixed- versus variable-dose Prothrombin Complex Concentrate for the emergent reversal of vitamin K antagonists: A systematic review and meta-analysis. *Crit Care Med*. 2024;52(5):811-820. doi:10.1097/CCM.0000000000006212
18. Khorsand N, Giepmans L, Meijer K, van Hest RM, Veeger NJ. A low fixed dose of prothrombin complex concentrate is cost effective in emergency reversal of vitamin K antagonists. *Haematologica*. 2013;98(6):e65-e67. doi:10.3324/haematol.2013.085043