

*Bruno Riou, M.D., Ph.D., Editor*

## Case Scenario: Emergency Reversal of Oral Anticoagulation

Aristides Koutrouvelis, M.D.,\* Amr Abouleish, M.D., M.B.A.,† Alexander Indrikovs, M.D., M.B.A.,‡ Jack Alperin, M.D.§

**R**EVERSING warfarin-induced anticoagulation quickly and effectively can be challenging in medically compromised patients presenting for emergency surgery. Anticoagulation reversal poses a delicate balance between increasing the risk of clotting and decreasing the risk of intraoperative blood loss. Furthermore, variable individual responses and warfarin's adverse effect profile render particular dosing challenges. Consequently, meticulous monitoring of anticoagulated patients with prothrombin time and international normalized ratio (INR) must guide titration.<sup>1</sup>

Traditionally, fresh frozen plasma (FFP) has been the mainstay of warfarin reversal.<sup>2</sup> Herein, we present a case in which we administered prothrombin complex concentrate (PCC) instead of FFP to hasten INR correction, reduce volume requirements, and diminish immune-related risks.

### Case Report

A 72-yr-old white man with a history of renal insufficiency, deep vein thrombosis 6 months before, and previous chemotherapy and radiation therapy for prostate cancer presented for emergent repeat laparotomy for ureteral and bowel obstruction. The patient had been on warfarin until 2 days before the surgery and presented to the holding area with an INR of 5.0. The primary team had administered 5 mg vitamin K intravenously 1 h before the planned procedure. After

consulting with a hematologist, we chose to administer Profilnine SD (Grifols Biologicals, Inc., Los Angeles, CA),<sup>3</sup> a PCC, for reversal of warfarin in lieu of FFP. After an intravenous dose of PCC 20 IU/kg, given over 10 min, the INR corrected to 1.5 within 30 min. The 2-h operation proceeded uneventfully without transfusion of blood products. The patient was placed on low molecular weight heparin within 24 h after the operation. Warfarin therapy was resumed on postoperative day 2. The patient was discharged with an INR of 2.5 without any significant episodes of perioperative bleeding or clotting.

### Discussion

Important issues to consider in this case include the following:

#### 1. What Are the Preoperative Hemostatic Goals?

Although the patient in this scenario was not actively bleeding, the likelihood of encountering surgical bleeding was very high—as was the risk of postoperative thrombosis. Furthermore, as a result of the emergent nature of the surgery, timely reversal of anticoagulation was essential. With an initial INR of 5.0, both the effectiveness of clotting factors and the volume load of the reversal regimen were of concern. The degree of anticoagulation, which is assessed by the INR, is effected by warfarin dosing, the presence of endogenous vitamin K, and the underlying ability of the liver to produce coagulation factors. Also of concern was the patient's renal impairment, which further contributes to coagulopathy from the resultant platelet dysfunction. Alternatively, ongoing inflammation and cancer can increase the potential for thromboembolism. Our aim was to facilitate a safe and expedient perioperative course, avoid bleeding and thrombosis, and achieve timely and acceptable INR reduction while minimizing adverse immune-mediated events and avoiding fluid overload.

#### 2. How Does Warfarin Inhibition of Vitamin K Induce Anticoagulation?

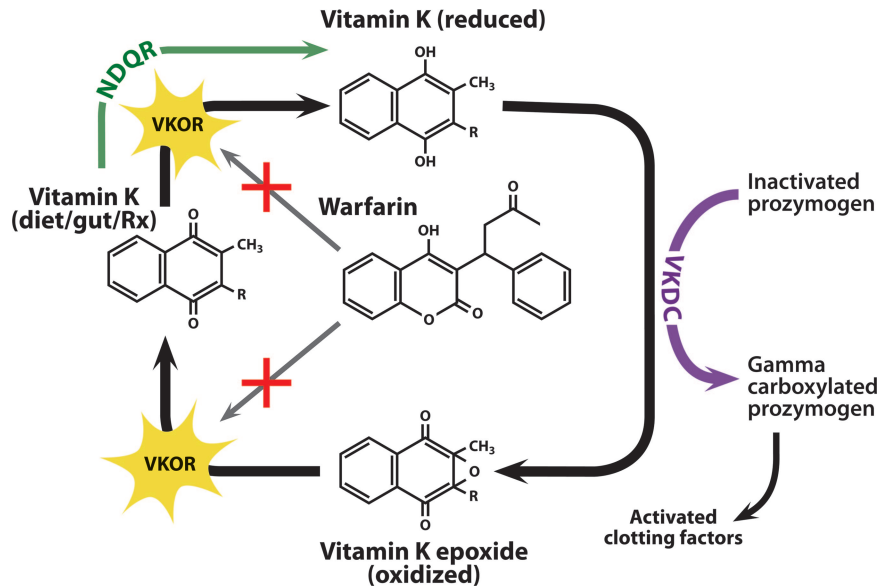
Vitamin K is required for proper blood clotting (fig. 1). Reduced vitamin K is necessary for carboxylating certain glutamic acid residues of many coagulation proteins. The resultant  $\gamma$ -carboxylated coagulation factors, which are required for binding calcium on negatively

\* Associate Professor, † Professor, Department of Anesthesiology, ‡ Professor, Department of Pathology, Director, Blood Bank, § Professor, Division of Hematology/Oncology, Departments of Internal Medicine and Anesthesiology, School of Medicine, University of Texas Medical Branch at Galveston, Galveston, Texas.

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Address correspondence to Dr. Koutrouvelis: Department of Anesthesiology, University of Texas Medical Branch, Route 0591, Galveston, Texas 77555-0591. arkoutro@utmb.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

**Fig. 1.** Coagulation pathway and location of warfarin action. Warfarin, which is structurally similar to vitamin K, acts by inhibiting vitamin K epoxide reductase—an enzyme in the vitamin K cycle—whose inhibition decreases clotting. To some degree, it also inhibits vitamin K reductase. These enzymes, inhibited by warfarin, are essential for a number of the procoagulation factors (II, VII, IX, and X) as well as anticoagulation proteins C, S, and Z. NDQR = NADPH:quinone reductase; VKOR = vitamin K epoxide reductase; VKDC = vitamin K dependent carboxylase.



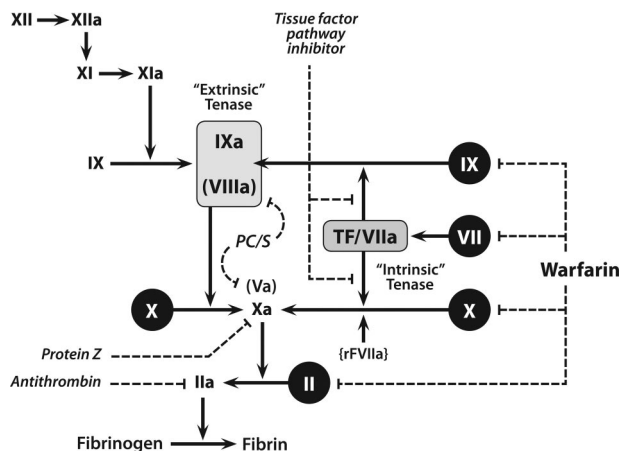
charged phospholipid surfaces, ensure a procoagulant effect leading to clotting. Inhibition of vitamin K by warfarin leads to an anticoagulant effect. Warfarin specifically impedes the enzyme vitamin epoxide reductase from forming vitamin K, a cofactor essential for the posttranslational  $\gamma$ -carboxylation of several blood coagulation factors. Consequently, the prozymogens in the presence of warfarin are rendered neither  $\gamma$ -carboxylated nor activated.<sup>4</sup> These reductase enzymes are essential for coagulation factors II, VII, IX, and X, as well as proteins C, S, and Z, which are essential to bring about the physiologic clotting process, as depicted in the coagulation cascade (fig. 2).<sup>5</sup> The net effect is that warfarin will make a patient less likely to clot and more likely to bleed. The temporal procoagulant or anticoagulant effect depends on the relative concentration and the

half-lives of the procoagulant and anticoagulant proteins at the time of, and throughout the duration of, warfarin administration. It is noteworthy that an INR higher than 3.5 typically correlates with only 10% of vitamin K–dependent factor activity and treads dangerously into the realm of bleeding.<sup>6</sup>

### 3. What Are the Options for Urgent Reversal?

The choices to reverse the anticoagulant effect of warfarin in an elective setting are distinct from those in an emergency setting. In an elective case when there is sufficient time, warfarin is typically withheld for 4–5 days because of its long half-life. An anticoagulant with a shorter half-life, such as heparin, is often initiated as a “bridging therapy” in the patient with high- to moderate-risk thrombosis. Heparin is then discontinued on the day of surgery. When less time (less than 24 h) is available, oral vitamin K can be administered and may normalize the INR within 24 h, although its efficacy and pharmacokinetics vary depending on the manufacturer. When even less time is available—as in the urgent and emergent setting—intravenous vitamin K may be given. It will take only 4–6 h to begin restoring the coagulation factors to functional levels.<sup>7</sup> Finally, replacing clotting factors will further speed the reversal of warfarin’s anticoagulant effect.

*In an emergency setting, cessation of warfarin, supplementation with vitamin K, and replacement of factors must be combined.* Factor VII, which is present in FFP and PCC, has a short half-life of roughly 4 h. For this reason, it must be combined with vitamin K, which also permits restoration of functional endogenous factor VII concentrations. Through these combined mechanisms, vitamin K helps maintain a normal INR (less than 1.5) postoperatively. Therapies to reverse warfarin include FFP, PCC, and recombinant factor VIIa (rFactor VIIa). However, both PCC and rFactor VIIa represent off-label use for this setting in the United States.<sup>8,9</sup> Although hemostasis management of anticoagulated patients lacks consensus, there has been a re-



**Fig. 2.** The coagulation cascade. The coagulation factors lead to the production of thrombin (IIa), which converts fibrinogen to fibrin. Warfarin inhibits the vitamin K–dependent factors II, VII, IX, and X. Natural anticoagulant mechanisms (underlined) are shown with dotted lines. Action of recombinant factor VIIa shown in brackets.

cent trend toward using PCCs for warfarin reversal. Clinical trials comparing PCC and FFP are ongoing. One *ex vivo* study that compared FFP, rFactor VIIa, and PCC demonstrated more consistent thrombin generation and faster INR restoration with PCC.<sup>10</sup> To date, no randomized clinical trials have been performed to compare warfarin reversal options in the emergency setting of bleeding or nonbleeding anticoagulated patients. Both rFactor VIIa and PCC have been used in neurosurgical emergencies, but head-to-head comparisons have not been performed.

#### 4. What Is PCC?

PCC is a lyophilized combination of concentrates of prothrombin, proconvertin, Stuart factor, and antihemophilic factor B (factors II, VII, IX, and X) derived from pooled plasma, as well as some anticoagulants. The U.S. Food and Drug Administration has approved the use of PCC for the prevention and control of bleeding in patients with hemophilia B as a result of factor IX deficiency. PCC has yet to be approved in the United States for use in warfarin reversal or INR normalization. It is, however, approved for this use in Europe.

Historically, PCCs have been categorized as three- or four-factor products based on low concentrations or the absence of factor VII (proconvertin). Two PCC products that were entirely lacking factor VII are no longer manufactured. Few available PCC preparations remain that are absent factor VII. One of these is Prothrombinex-HT, produced in Australia. It is normally supplemented with FFP-containing factor VII for INR normalization. Several other PCCs traditionally have been called three-factor products, but, like Profilnine, do in fact contain low concentrations of factor VII (35%) relative to factor IX.

When reconstituted, PCC is ready for infusion within minutes. A dose of 10–40 IU/kg over 5–15 min is adequate for warfarin reversal in most settings.<sup>11</sup> In such settings, recommendations also include the administration of vitamin K to maintain coagulation after labile coagulation factors are transfused and consumed.<sup>12</sup>

In our case scenario, the patient was at risk for poor absorption of vitamin K as a result of previous radiation therapy, which

also may have led to higher-than-expected INR with warfarin dosing. Similarly, in hospitalized patients who are ordered *nil per os* for an extended time, the patient may have little or no intestinal source of vitamin K. From a nutritional standpoint, the common use of antibiotics may to a large degree attenuate any endogenous bacterial flora necessary for the production and subsequent uptake of vitamin product from the gut. Vitamin K was not chosen as sole therapy for this patient because of his emergent care status. Although FFP was considered, we chose PCC (factors II, VII, IX, X) with vitamin K, a therapeutic option that provided rapid correction (within 30 min) after slow intravenous administration, per manufacturer instructions.

#### Comparison of PCC, FFP, and rFactor VIIa when Reversing Warfarin for Emergency Surgery

##### 5. Is There a Difference in Timing of Reversal?

INR will normalize in 4 days if warfarin is simply discontinued.<sup>13</sup> Alternatively, INR will normalize more quickly with vitamin K, approximately 24 h with oral administration and 6–12 h with intravenous administration. Unfortunately, for emergency surgery, these options are simply not viable (table 1).

For emergency surgery, PCC and FFP are the two main options. Recently, rFactor VIIa has also been used. PCC needs to be reconstituted, but this can be accomplished within minutes. Intravenous administration of PCC over 5–10 min often corrects INR within 30 min.<sup>14,15</sup> Hence, PCC will normalize INR well within 60 min. In contrast, FFP often is not even available for administration within 60 min because of the need for ABO blood typing, FFP thawing, and transport from the blood bank. Further, because FFP volume is possibly larger, requiring more than a liter for a 70 kg patient (10–20 ml/kg), infusion at 400 ml/h (to avoid fluid overload) may take longer than 2 h to complete.<sup>16</sup> rFactor VIIa, alternatively, can be given via bolus dosing and repeated at 2 h (as necessary) or by constant infusion, but it is usually restricted in most hospital formularies

**Table 1.** Comparison of PCC, FFP and Factor VIIa when Reversing Warfarin for Emergency Surgery

	Time for Normalizing INR (Includes preparation and Administration)	Immune Issues	Hemostasis	Volume
PCC	<60 minutes	<ul style="list-style-type: none"> <li>• Virally deactivated</li> <li>• no RBCs</li> </ul>	Quantified levels of factors	<100 ml
FFP	>2 hours, depending on amount transfused and rate of transfusion	<ul style="list-style-type: none"> <li>• ABO crossmatch</li> <li>• TRALI</li> </ul>	Factor concentrations are not quantified and may vary	May need 15 to 20 ml/kg
Factor VIIa	<60 minutes	Minimal	Risk of clot/thromboembolism	<100 ml

PCC = Prothrombin Complex Concentrate; FFP = Fresh Frozen Plasma; INR = international normalized ratio; RBC = red blood cells; TRALI = transfusion related acute lung injury.

and requires a hematology consultation, which may take up to 30 min.

#### 6. Which Offers a Better Hemostasis Balance?

There have been few prospective randomized trials comparing FFP and PCC safety and efficacy. Studies have shown that FFP is inferior to PCC in reliably reversing INR as demonstrated by the inability of even up to 800 ml FFP to restore clotting factors to normal concentrations compared with PCC (25–50 IU/kg).<sup>17</sup> For a comprehensive procoagulant effect, FFP may be considered, but for surgical procedures and postoperative requirements, PCC may be the better alternative for warfarin reversal. FFP restores not only the coagulation factors affected by warfarin but also all of the coagulation factors and proteins present in human plasma. In a patient with preexisting undiagnosed non-vitamin K-dependent factor deficiency, FFP may have an advantage.

Previous deep vein thrombosis mandates long-term anticoagulation to minimize risk of recurrent deep vein thrombosis and to avoid life-threatening pulmonary embolism. The risk of administering procoagulant agents is significantly increased by thrombotic history, which is why a three-factor product, which typically has less than 35% of the factor IX concentration, may have distinct advantages over a four-factor product in reducing likelihood of embolism in this scenario. Alternatively, the suboptimal effect of correcting supratherapeutic INR with three-factor product has been called into question.<sup>18</sup> This “suboptimal effect” may lean toward a bleeding tendency, but many would consider it an acceptable risk in light of the fact that many perioperative bleeding episodes are considered less dangerous than clotting episodes (myocardial infarction, stroke, pulmonary embolus). Postoperative thrombotic risk may be principally bound to thrombin, which is both in PCC and FFP. In addition, the long half-life of thrombin should be carefully considered in repeated prescriptions of these agents.

Despite the lack of marketed indication, rFactor VIIa has been used off-label for warfarin reversal in several case reports and retrospective cohort studies.<sup>25–27</sup> Of concern to some clinicians is the fact that rFactor VIIa, as an activated product, may be particularly dangerous in patients predisposed to embolus.<sup>28</sup> Yet, rFactor VIIa’s hemostatic effect in situations where there are low factor levels may make clotting difficult.<sup>29,30</sup> The exact mechanisms of rFactor VIIa are still under investigation.

#### 7. What Are the Immune-related Risks?

Transfusion reactions and infections are the main concern. Although PCC is derived from pooled human plasma, it is solvent detergent-treated to reduce the risk of transmission of viral infections. Hence, it carries less risk of infection than FFP. Transfusion-related acute lung injury (TRALI), particularly from centers using female donors, carries a significant risk associated with the infusion of blood products,

particularly FFP. Because blood products contain proteins that induce immune triggers, the potential for anaphylaxis and allergic reactions exists for both PCC and FFP. Immunomodulatory risk accompanies the transfusion of blood and blood products, impairing immune surveillance, which may be even more concerning in patients with history of cancer. FFP contains isohe-magglutinins, requiring vigilance in ABO evaluation—a necessary step to avoid blood-type incompatibility and immune-mediated hemolysis, although clerical errors may still occur. Like PCC, rFactor VIIa has minimal virally associated risks and no reported incidence of TRALI.

#### 8. What Is the Aggregate Cost Comparison?

The largest vial of Profilnine (1,500 units) costs \$1,140. One unit of FFP (approximately 250 ml) costs \$93 and the average dose is 15 ml/kg. In a 100 kg patient, 6 units would cost around \$651, which includes \$93 for blood typing. Costs of reversal therapy may be higher if complications from administration of PCC (e.g., thromboembolism) or FFP (e.g., TRALI) develop. However, a formal cost-analysis comparison of the two modalities, as well as a randomized comparative trial, has not been done. At this time, rFactor VIIa is the most expensive of the three regimens—and has yet to be proven the most effective option for warfarin reversal.

#### 9. What Are the Current Guidelines?

Although there are guidelines for the warfarin reversal in elective surgery, there are no uniform guidelines for reversal in the emergency setting. Geographic differences in the availability of PCC preparations partially account for variations among international practice guidelines. Monitoring of anticoagulation and reversal are typically assessed with INR, although there have been a few recommendations for monitoring coagulation with thrombin generation and thromboelastography.<sup>31,32</sup> Below are some guidelines to using PCC.

**Guidelines in the United States.** For elective surgery, the American College of Chest Physicians/CHEST guidelines<sup>19</sup> suggests either adjusting warfarin for low-risk bleeding procedures to target an INR between 1.3 and 1.5—or withholding warfarin altogether, depending on thrombotic risk stratification. Although not specific to the emergency setting, the recommendation for “serious bleeding at any elevation of INR” in the recommendations is to hold warfarin therapy and provide vitamin K (10 mg by slow intravenous infusion), supplemented with fresh plasma or PCC, depending on the urgency of the situation. In addition, rFactor VIIa may be considered as alternative to PCC, and vitamin K can be repeated every 12 h (Grade 1C). Similarly, the CHEST guidelines<sup>19</sup> also refer to “life-threatening bleeding,” advising withholding warfarin therapy and providing FFP, PCC, or rFactor VIIa supplemented with 10 mg vitamin K slowly intravenously (Grade 1C). Current guidelines in the United States do not specify which PCC products should be used.



**Guidelines in Australasia.** Prothrombinex-HT<sup>20</sup> (CSL Limited, Parkville, Victoria, Australia) is the only PCC approved in Australia and New Zealand for warfarin reversal. It is a true three-factor product containing primarily II, IX, and X, but no factor VII. For this reason, FFP, which contains increased concentrations of factor VII, is recommended as adjuvant to Prothrombinex-HT when used for warfarin reversal.<sup>14</sup> For patients with low-risk thromboembolism, if INR is higher than 1.5 and if surgery is urgent, recommendations are for Prothrombinex-HT (25–50 IU/kg) plus 150–300 ml FFP, or 10–15 ml/kg FFP if Prothrombinex-HT is not used. For high-risk thrombotic events and emergency surgery, there are no clear recommendations.

**Comment from Dr. Alperin, Division of Hematology/Oncology, Departments of Internal Medicine and Anesthesiology, School of Medicine, University of Texas Medical Branch at Galveston.**

This paper describes a relatively new therapeutic approach when patients are being treated with the anticoagulant warfarin and require immediate surgery. The coagulopathy caused by warfarin, a vitamin K antagonist, must be corrected quickly to avoid excessive intraoperative bleeding. The approach described herein has proved effective and safe.

The authors took a different approach by giving the patient a PCC, originally indicated for hemophilia B. Derived from human plasma, PPC contains vitamin K–dependent coagulation factors in a concentrated form. The proprietary name of the PPC used is Profilnine, which is one of two PCCs available in the United States. Profilnine offers a number of advantages over treatment with FFP: a smaller volume is needed; the clotting factors are dissolved in water rather than plasma; and the concentrate can be prepared more quickly, is more easily administered, and is associated with fewer risks. Profilnine differs from Feiba (Baxter AG, Vienna, Austria), another factor product that contains the activated form of factor VII and is used in primarily in patients with hemophilia.

After warfarin administration, protein C and S are quickly inhibited because of their relatively low concentrations compared with factors II, VII, IX, and X in blood, thereby accounting for the “paradoxical” early prothrombotic potential of the drug, particularly in patients with known thrombophilia. It is precisely for this reason that heparin (intravenous or low molecular weight heparin) is often administered before the initiation of warfarin or concurrently for days of warfarin therapy.<sup>21</sup>

An argument against using rFactor VIIa prophylactically is that it is an activated factor and the thrombotic risk may be greater than PCC, although there are no studies that demonstrate such. For this reason, most clinicians reserve off-label use for actively bleeding patients only. rFactor VIIa is indicated in hemophilia B with inhibitors and factor VII–deficiency because of low risk of viral transmission, risk of thromboembolus, and anaphylactic reactions in patients with bovine protein allergy. Dose between 15–90  $\mu\text{g/kg}$  with redosing as necessary every 2 h or a 50  $\mu\text{g/kg/h}$  infusion. It is noteworthy that platelets and

fibrinogen must be present in adequate amounts to ensure the coagulation efficacy of rFactor VIIa.

**Comment from Dr. Indrikovs, Department of Pathology and Director, Blood Bank, School of Medicine, University of Texas Medical Branch at Galveston.** A significant proportion, 25–50%, of all FFP used in U.S. blood banks is employed for warfarin reversal. TRALI, particularly in the context of FFP from female blood donors, is a significant risk associated with the infusion of blood components. Women are able to make anti-HLA and/or antineutrophil antibodies when exposed during pregnancy to foreign (paternal) fetal antigens. A greater number of pregnancies corresponds with a higher rate of antibody formation. Approximately 20–25% of women with two or more pregnancies have antibodies that, when transfused to a patient with the corresponding HLA or neutrophil antigens, can cause TRALI.

Other serious hazards of transfusion—including viral and bacterial infections, anaphylaxis, and other types of acute transfusion reactions, immune hemolysis, and immunomodulation—must always be considered when making decisions to transfuse plasma. Not to do so is an abuse of products, particularly with the increase in TRALI and its serious consequences.

## Knowledge Gap

This case demonstrates the complexities of hemostatic balance and choices made in balancing the conflicting goals of averting bleeding and thrombosis, achieving timely and effective reversal, minimizing immune risks, and avoiding fluid overload in the emergency setting. We have described the potential value of choosing PCC instead of the more commonly used FFP in the emergent reversal of an anticoagulated patient on warfarin. The amount of factor concentrations in the various available PCCs around the world varies with respect the procoagulant and anticoagulant contents. No randomized studies have compared three- and four-factor products. Consequently, not all PCCs are the same. Most “three-factor products” actually contain factor VII—as does Profilnine—but in relatively small doses (roughly one third that of factor IX). This inconsistency makes the interpretation and application of current international guidelines difficult because it is not always clear which “prothrombin concentrate” authors are referring to within these documents.

Despite variations in the concentration of factors of various products, the specific factor concentrations of PCC are quantified, particularly with respect to factor IX, unlike the unknown variability of factors in each unit of FFP. Recently, the use of PCC use in emergent neurosurgical and cardiothoracic procedures has been studied,<sup>22–24</sup> demonstrating rapid correction of drug-induced coagulopathy.

Although each clinical scenario is unique, future clinical outcomes in emergency anticoagulation reversal are necessary to help prescribe appropriate hemostatic agents with known coagulation values. Such studies will guide clinicians to optimize hemostasis in a variety of medical and surgical

contexts, minimizing perioperative and long-term thrombosis in a more methodical manner. Logistic and ethical challenges add to the difficulty in recruiting and consenting of anticoagulated patients in the emergency care setting. Collaborative approaches among anesthesiologists, surgeons, and hematologists, as well as blood bank and pharmacy staff, are essential for efficient medical management.

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