Coagulation Cocktails: Helpful Hints and Hard Data for Perioperative Bleeding

Jerrold H Levy, MD, FAHA
Professor of Anesthesiology, Deputy Chair Research, Emory University School of Medicine and Emory Healthcare, Atlanta, Georgia

INTRODUCTION

Patients in a perioperative setting often receive anticoagulation for multiple reasons that include atrial fibrillation and ischemic cardiovascular disease. In patients with an acute coronary syndrome, following percutaneous coronary interventions, or with an acute ischemic stroke, the rupture or injury of an atherosclerotic arterial plaque serves as a nidus for platelet aggregation and thrombus formation, which, in turn, may cause myocardial infarction, stroke, or death. Activation and expression of the glycoprotein IIb/IIIa receptor (where fibrinogen binds) on platelets leads platelet aggregation and thrombus formation. When this receptor is activated, circulating fibrinogen binds to it and cross-links with adjacent platelets to create a platelet–fibrinogen matrix. Since platelets have a pivotal role in the pathogenesis of thrombosis after plaque rupture, antiplatelet agents including aspirin, thienopyridines (clopidogrel, prasugrel, ticagrelor), and the glycoprotein IIb/IIIa inhibitors, reduce adverse events that are associated with plaque rupture.

As a result, patients often present for surgery with underlying hemostatic disorders because of preexisting preoperative anticoagulation or antiplatelet therapy. Patients may also present receiving anticoagulation therapy for reasons that include atrial fibrillation, venous thrombosis prophylaxis, prosthetic valves, or for coronary artery disease. All therapies that prevent clot from forming in pathologic states, also interfere with normal hemostasis, an important mechanism to protect patients from exsanguination.

OVERVIEW OF HEMOSTASIS

Hemostasis is also a far more complex system than intrinsic and extrinsic hemostatic activation as taught in medical school. Multiple factors are responsible for stopping bleeding including release of tissue factor, and generation of factor VIIa, platelet activation, and the complex cellular and humoral amplification that follows. There is a complex equilibrium between blood cells, platelets, coagulation factors, natural inhibitors of coagulation, and the fibrinolytic system. Surgical patients will develop acquired hemostatic changes that contribute to postoperative bleeding that include activation of the coagulation, fibrinolytic, and inflammatory pathways. Even healthy patients can develop coagulopathy following massive hemorrhage and/or tissue injury following trauma, surgery, or in an obstetrical population. The increasing use of low-molecular weight heparins (LMWH), oral anticoagulants (warfarin and new oral agents rivaroxaban and dabigatran), platelet inhibitors (thienopyridines-clopidogrel, prasugrel or ticagrelor), or direct thrombin inhibitors (r-hirudin, bivalirudin, argatroban), also may potentiate bleeding. This review will focus on current pharmacologic anticoagulation therapies surgical patients may receive and therapeutic perioperative and prohemostatic pharmacologic approaches that are used to treat or prevent bleeding in this setting.

ANTICOAGULATION

Anticoagulation is based on inhibiting both thrombin activation and platelet activation. Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further increase generation of thrombin. Because of the complex humoral amplification system linking both hemostatic and inflammatory responses, there are multiple pathways to produce thrombin and prothrombotic effects. Anticoagulation is based on inhibiting both thrombin activation and platelet activation. Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further increase generation of thrombin. Current and future anticoagulants used to prevent clot formation will be considered.

HEPARIN

Heparin, the most commonly used anticoagulant, is isolated from porcine intestine where it is stored in the mast cell granules. Unfractionated heparin (UFH) is a diverse mixture of 3000 to 30,000 dalton fragments. Heparin binds to antithrombin III (also called antithrombin or AT) increasing the rate of thrombin-AT III complex formation, but also inhibits other steps in coagulation. Advantages of heparin anticoagulation is that it can be reversed immediately by protamine and has a relatively shorter half life compared to other agents. UFH is also an important cause of heparin induced thrombocytopenia that can occur ~1-3% of patients who receive it.

LOW-MOLECULAR-WEIGHT HEPARINS (LMWH)

Like UFH, low-molecular-weight heparins (LMWHs) are glycosaminoglycans purified from UFH to a molecular weight ~5000. LMWHs have a longer half-life, and in patients with renal dysfunction, the effects can be greatly prolonged and should be avoided.
in this setting. Commonly used LMWHs include enoxaparin and dalteparin, and generic agents will be available soon.

SYNTHETIC XA INHIBITORS (FONDAPARINUX)

Fondaparinux is a synthetic antithrombotic agent with specific antiXa activity. Its pharmacokinetic properties allow for a simple, fixed-dose, once-daily regimen of subcutaneous injection, without the need for monitoring. This agent also has a long half and should be avoided with renal dysfunction.24

ORAL ANTICOAGULANTS:

Vitamin K Antagonists: warfarin

Warfarin has been the only oral agent available until recent approval of new agents that follow. Disadvantages of warfarin include delayed onset of action, the need for regular laboratory monitoring, difficulty in reversal should a surgical procedure create concern about bleeding.23 Warfarin inhibits an enzymatic process of vitamin K epoxide reductase that converts the vitamin K-dependent coagulation proteins (factors II (prothrombin), VII, IX, and X) to their active form, a posttranslational modification and as a result warfarin is called a vitamin K antagonist (VKA). Peak effects of warfarin do not occur for 36 to 72 hours because of its mechanism of action.23

Warfarin Management Before Elective Surgery

In patients receiving warfarin, the INR should be checked preoperatively. Although minor surgical procedures can be safely performed in patients receiving oral anticoagulants, for major surgery, discontinuation of oral anticoagulants preoperatively is recommended. Patients with prosthetic heart valves will often require bridging with UFH.25 Bleeding is the main complication of any anticoagulant therapy. Vitamin K will not immediately reverse the anticoagulant effect and additional therapies are needed as detailed in the guidelines for perioperative management by Douketis in the ACCP guidelines and summarized as follows in Perioperative Management of Antithrombotic Therapy.26

...The newer oral agents have a rapid onset with therapeutic anticoagulation within hours of administration and do not require routine monitoring. Dabigatran is an oral direct thrombin inhibitor, and rivaroxaban is a direct factor Xa inhibitor similar to low molecular weight heparin but independent of ATIII.24 Both of the newer agents require dose adjustments for renal failure and will be considered separately, along with agents under investigation.24,27

Dabigatran Eteixilate (Pradaxa)

Dabigatran etexilate is an oral, direct thrombin inhibitor approved for the prevention of stroke with atrial fibrillation that has a rapid onset of action, no requirement for routine coagulation monitoring, and approved outside of the US for the prevention of VTE after total hip or knee replacement surgery. Dabigatran’s effects can be measured best by thrombin times and also by aPTT values, although thrombin times are preferred.22 Dosing should also be adjusted for patients with renal dysfunction.

Rivaroxaban (Xarelto)

Rivaroxaban is an oral, direct Factor Xa inhibitor that does not require antithrombin as a co-factor. Direct Factor Xa inhibitors, including rivaroxaban, apixiban, and edoxaban can inhibit free Factor Xa, clot Xa and Factor Xa bound to the prothrombinase complex. Rivaroxaban is approved in the US and elsewhere for stroke prevention for atrial fibrillation and for the prevention of VTE in adult patients after elective hip or knee replacement surgery, based on large clinical trials where rivaroxaban was compared to warfarin or enoxaparin respectively, while apixiban is being reviewed.24,27

Perioperative Management of the New Oral Anticoagulants

In the US, warfarin is still a problem for clinicians because the balanced prothrombin complex concentrates (PCCs) that contain all four factors (II, VII, IX, X) like Beriplex and Octaplex for immediate INR reversal are not available.28 Vitamin K takes days to work, ~4 units of fresh frozen plasma (FFP) is required with transfusion risk issues and volume overload, and FFP never restores the INR to baseline but usually to ~1.4-1.6 which is the baseline INR for FFP.28

The French Study Group on thrombosis and hemostasis have proposed perioperative management strategies.29 They suggest for procedures with low hemorrhagic risk, a therapeutic window of 48 hours (last administration 24 hours before surgery, restart 24 hours after) is proposed. For procedures with medium or high hemorrhagic risk, they suggest stopping therapy 5 days before surgery to ensure complete elimination in all patients. Treatment should be resumed only when the risk of bleeding has been controlled. In patients at high thrombotic risk (e.g. those in atrial fibrillation with a history of stroke), bridging with heparin is proposed. They suggest prohemostatic agents should not be given for prophylactic reversal due to their uncertain benefit-risk.29

Monitoring the New Oral Anticoagulants

Although routine monitoring of the new anticoagulants is not standard, if needed they can be evaluated with specialized tests. For dabigatran, thrombin clotting time (TT), ecarin clotting time (ECT), and activated partial thromboplastin time (aPTT) can measure its effects.30 The aPTT potentially provides a qualitative assessment of anticoagulation. Although there is no specific antidote to antagonize the anticoagulant effect of dabigatran, because of its short duration of effect drug discontinuation should be considered as previously noted. With overdose,
dabigatran can also be dialyzed in patients with renal impairment. In instances of life-threatening bleeding, prohemostatic agents such as PCCs can be considered. For rivaroxaban prolongation of most standard hemostatic tests are too variable and specialized tests evaluating antiXa are required. Recent data also suggests PCCs completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but only partially reverses dabigatran at the PCC doses of 50 IU/kg used in the study. Dabigatran can also be dialyzed.

In summary, for those who require urgent surgery, managing patients who receive dabigatran, rivaroxaban and other novel oral anticoagulants require cessation of the drug. However, risk versus benefit considerations need to be considered. It is important to note the therapies for reversal are off label uses from the literature as referenced, but provide important perspective for perioperative management for the clinician faced with managing patients receiving these agents.

**USE OF NEW ANTICOAGULANTS FOR NEURAXIAL ANESTHESIA**

When used with neuraxial anesthesia, an epidural catheter should not be removed earlier than 18 hours after the last administration of rivaroxaban, and the next rivaroxaban dose should be administered no earlier than 6 hours after the removal of the catheter and as noted in the package insert (http://www.xareltohcp.com/sites/default/files/pdf/xarelto_0.pdf#zoom=100). Recommendations for dabigatran suggest the risk of spinal or epidural hematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate. These patients require frequent observation for neurological signs and symptoms of spinal or epidural hematoma. (http://www.cema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf)

**PLATELET INHIBITORS**

In patients with myocardial ischemia and/or atherosclerotic vascular disease, inhibiting platelet activation is critical in managing these patients. Platelet inhibitors/antiplatelet agents should also be considered as anticoagulants, and also pose increased risks for bleeding. The antiplatelet agents differ in their modes of action, potency, onsets of action, and indications. Aspirin irreversibly inhibits platelet cyclooxygenase and thromboxane A2, a platelet activator. Aspirin is a relatively weak antiplatelet agent. Nonsteroidal anti-inflammatory drugs also reversibly inhibit cyclooxygenase. Aspirin, however, irreversibly alters the cyclooxygenase so that platelet pool is destroyed until effective replacement occurs from the bone marrow, however resistance can occur. More potent antiplatelet agents include clopidogrel (Plavix) and IIb/IIIa receptor antagonists (abciximab, tirofiban, eptifibatide). Clopidogrel, prasugrel, and ticagrelor are more potent than aspirin, and inhibit platelets by selectively and irreversibly binding to the P2Y12 receptor to inhibit the adenosine diphosphate–dependent pathway of glycoprotein IIb/IIIa–receptor activation although resistance can occur. Clopidogrel is the major agent used with the least knowledge available about how to manage these patients or monitor its effects.

Antiplatelet therapy with aspirin and clopidogrel is standard care following revascularization by percutaneous coronary intervention with stent insertion. This so-called dual therapy is recommended for up to 4 weeks after intervention for bare-metal stents and for 6-12 months after intervention for drug-eluting stents. Vincenzi noted a 45% complication rate and a mortality of 20% reported in patients undergoing noncardiac surgery after coronary artery stenting. Discontinuation of antiplatelet drugs appeared to be of major influence on outcome. They prospectively evaluated 103 patients receiving stents within 1 year before noncardiac surgery. Antiplatelet drug therapy was not, or only briefly, interrupted. Heparin was administered to all patients. Of 103 patients, 44.7% developed complications after surgery; 49.9% of the patients died. All but two (bleeding only) adverse events were of cardiac nature. Most complications occurred early after surgery. The risk of suffering an event was 2.11-fold greater in patients with recent stents (<35 days before surgery) compared with percutaneous cardiac intervention more than 90 days before surgery. The clopidogrel package insert suggests if a patient is to undergo elective surgery and an antiplatelet effect is not desired, it should be stopped 5 days before surgery. However, if patients bleed, therapy or monitoring its effects has not been established. Further, the risk compared to the benefit of stopping clopidogrel, need to be weighed against the risk of stent thrombosis, and the need for surgical intervention as well.

Prasugrel has an advantage of increased potency and potentially a lower rate of “resistance”, one of the potential problems for clopidogrel.

**PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY BASED ON GUIDELINES**

Recent guidelines from the American College of Chest Physicians in 2012 have been reported. In patients requiring vitamin K antagonist (VKA) interruption before surgery, they recommend stopping VKAs 5 days before surgery instead of a shorter time before surgery (Grade 1B). In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, they suggest bridging anticoagulation instead of no bridging during VKA interruption (Grade 2C); in patients at low risk, they suggest no bridging instead of bridging (Grade 2C). In patients who require a dental procedure, they suggest continuing VKAs with an oral prohemostatic agent or stopping VKAs 2 to 3 days before the procedure instead of alternative strategies (Grade 2C).
In moderate- to high-risk patients who are receiving acetylsalicylic acid (ASA) and require noncardiac surgery, they suggest continuing ASA around the time of surgery instead of stopping ASA 7 to 10 days before surgery (Grade 2C). In patients with a coronary stent who require surgery, they recommend deferring surgery > 6 weeks after bare-metal stent placement and > 6 months after drug-eluting stent placement instead of undertaking surgery within these time periods (Grade 1C); in patients requiring surgery within 6 weeks of bare-metal stent placement or within 6 months of drug-eluting stent placement, they suggest continuing antiplatelet therapy perioperatively instead of stopping therapy 7 to 10 days before surgery (Grade 2C).

**PROCOAGULANT AGENTS**

Anesthesiologists are often called on to correct coagulopathy in patients who are actively bleeding despite transfusion and other therapies. Further, many patients may also have received any one or combination of the anticoagulant agents just reviewed. Therefore, clinicians must understand some of the potential procoagulant therapies available to reverse bleeding or anticoagulation therapy. These agents include antifibrinolytics, protamine, desmopressin, fibrinogen, purified protein concentrates, recombinant factor VIIa (rFVIIa)), and topical hemostatic agents, and each will be considered separately.

**ANTIFIBRINOLYTIC AGENTS**

Antifibrinolytic agents include Epsilon-Aminocaproic Acid (EACA) and Tranexamic Acid (TXA), and aprotinin. EACA and TXA are lysine analogs that competitively inhibit activation of plasminogen to reduce conversion of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. TXA also directly inhibits plasmin, but higher doses are required than are needed to reduce plasmin formation. The lysine analogs have variable effects on reducing bleeding, especially EACA, and published safety data on these agents are limited. Most of the efficacy data for these agents are reported with TXA, and represent small studies or from meta-analyses of pooled previously published data. Antifibrinolytic agents have also been reported for blood conservation in orthopedic and other surgical procedures.

One important TXA study is the CRASH2 study that evaluated safety and efficacy of TXA in 20,211 adult trauma patients randomized to 1 g load and infusion over 8 h to placebo. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All-cause mortality was significantly reduced with tranexamic acid (1463 [14.5%] tranexamic acid group vs 1613 [16.0%] placebo group; p=0.0035). The risk of death due to bleeding was significantly reduced (489 [4.9%] vs 574 [5.7%]; p=0.0077). TXA is also approved in the US for cyclic heavy menstrual bleeding at a dose of 3.9 g/day (Lysteda).

Aprotinin is a broad spectrum protease inhibitor and antifibrinolytic agent, originally approved for reducing bleeding in coronary surgery in the US, but removed from marketing in 2008 based on the BART study. However, recent reviews by the Canadian and European Union have concluded that aprotinin’s benefits in preventing blood loss outweigh its risks in patients undergoing isolated heart bypass surgery who are at high risk of major blood loss. Aprotinin was suspended following the preliminary results of the BART study, a randomized controlled trial in high-risk heart surgery patients. These results appeared to show an increased death rate in patients receiving aprotinin after 30 days compared to patients taking other medicines, and led to the early discontinuation of the study by its data safety monitoring board. Based on the final results of the BART study as well as the results of other clinical studies, data from the scientific literature, reports of side effects and information submitted by the companies that market antifibrinolytic medicines, the Committee found there were a number of problems with the way the BART study was conducted, which cast doubt on the previous conclusions. These included the imbalances in the way blood-thinning medicines such as heparin were used, inappropriate monitoring of the use of these medicines and how problems with the way that data from some patients were excluded from the initial analysis. The Committee found that the BART study’s results were not replicated in other studies and that the overall data available showed that aprotinin’s benefits is greater than its risks in the restricted indication.

**DESMOPRESSIN**

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that stimulates the release of ultralarge von Willebrand factor (vWF) multimers from endothelial cells. VWF mediates platelet adherence to vascular subendothelium by functioning as a protein bridge between glycoprotein Ib receptors on platelets and subendothelial vascular basement membrane proteins. DDAVP shortens the bleeding time of patients with mild forms of hemophilia A or von Willebrand disease. Surgical patients who might benefit from use of DDAVP are not clear. DDAVP is administered intravenously at a dose of 0.5 mg/kg, and should be given over 15-30 minutes to avoid hypotension. Most studies have not confirmed the early reported efficacy during complex cardiac surgery. Mannucci noted there have been 18 trials of desmopressin in 1295 patients undergoing cardiac surgery that show a small effect on perioperative blood loss (median decrease, 115 ml).
RECOMBINANT COAGULATION PRODUCTS

Recombinant coagulation products are used to manage bleeding in patients with hemophilia, von Willebrand’s disease (vWD), or acquired inhibitors to antihemophilic factor (e.g., AHF concentrates, factor IX concentrates, factor VIIa concentrate, factor IX complexes, anti-inhibitor coagulant complexes). Recombinant activated factor VIIa (rFVIIa; NovoSeven,® Novo Nordisk) is approved for hemophilia patients with inhibitors to treat bleeding. Currently, rFVIIa is used off label as a prohemostatic agent in complex clinical situations for life threatening hemorrhage.

Recombinant factor VIIa produces a prohemostatic effect by forming a complex with tissue factor (TF) that is expressed at the site of injury, and locally initiates hemostatic activation. TF is a membrane-bound glycoprotein that is expressed on subendothelial cells after tissue injury and loss of endothelial protective mechanisms. Circulating FVIIa accounts for nearly 1% of circulating FVII, and is inactive until bound with TF9. When rFVIIa is administered, it binds to TF that activates factor X to factor Xa, leading to the generation of thrombin (FIIa) and resulting fibrin formation and platelet activation. Giving rFVIIa to patients with multiple hemostatic abnormalities may result in added thrombin generation both on the surface of activated platelets but also at the local site of injury. Multiple publications report rFVIIa in surgical patients and cardiac surgical patients including a recent reported analysis of the clinical studies. Other publications have reported the cessation of bleeding following major trauma with refractory hemorrhage and coagulopathy. The therapeutic dose of rFVIIa in non hemophilia patients are not established. Guidelines as reported by Goodnough and Despotis for off label use in patients with life threatening hemorrhages.

We evaluated the rate of thromboembolic events in all published randomized, placebo-controlled trials of rFVIIa used on an off-label basis from 35 randomized clinical trials (26 studies involving patients and 9 studies involving healthy volunteers) to determine the frequency of thromboembolic events. Among 4468 subjects, 498 had thromboembolic events (11.1%). Rates of arterial thromboembolic events among all 4468 subjects were higher among those who received rFVIIa than among those who received placebo (5.5% vs. 3.2%, P=0.003). Rates of venous thromboembolic events were similar among subjects who received rFVIIa and those who received placebo (5.3% vs. 5.7%). Among subjects who received rFVIIa, 2.9% had coronary arterial thromboembolic events, as compared with 1.1% of those who received placebo (P=0.002). Rates of arterial thromboembolic events were higher among subjects who received rFVIIa than among subjects who received placebo, particularly among those who were 65 years of age or older (9.0% vs. 3.8%, P=0.003); the rates were especially high among subjects 75 years of age or older (10.8% vs. 4.1%, P=0.02). Overall, in a large and comprehensive cohort of persons in placebo-controlled trials of rFVIIa, treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events, especially among the elderly. Other major issues regarding rFVIIa include costs and dosing.

REVERSAL OF VITAMIN K ANTAGONISTS ASSOCIATED COAGULOPATHY

Prohemostatic agents are often needed to urgently reverse the anticoagulant effect of warfarin in the perioperative setting. Treatments available for reversal include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and rFVIIa. Warfarin reversal is becoming a major indication for FFP in some hospitals. PCCs were originally developed for repleting factor IX in hemophilia B, and contain standardized amount of FIX along with various amounts of other vitamin K dependent factors (prothrombin, FVII, FX, protein C and S). PCCs are recommended in guidelines as primary treatment for reversal in patients with life-threatening bleeding and an elevated international normalized ratio (INR), and rFVIIa may be considered as an alternative. Compared with FFP, evidence suggests PCCs offer quicker INR correction and improved bleeding control; they also have a lower infusion volume and are more readily available without cross matching. Although there are historical concerns regarding potential thrombotic risk with PCCs, present-day PCCs are much improved.

FIBRINOGEN

Fibrinogen is an under recognized coagulation factor critical for producing effective clot in surgical patients, and data supports it as a predictor of perioperative bleeding. During the third trimester of pregnancy, fibrinogen levels are elevated to >400 mg/dL. Bleeding increases for each 100 mg/dL decrease of fibrinogen expected to prevent bleeding. Fibrinogen can be replete by human plasma-derived fibrinogen concentrate; otherwise, fibrinogen-rich cryoprecipitate can be given (one unit per 10-kg increases fibrinogen by 50–70 mg/dL). In Europe, fibrinogen concentrates are available and cryoprecipitate is not used. A fibrinogen concentrate (RiaSTAP, CSL Behring) has just been granted licensing as an orphan drug for treating bleeding in patients with congenital afibrinogenemia or hypofibrinogenemia, but not for patients with dysfibrinogenemia. Data to support the approval came from a study of 15 patients with afibrinogenemia who received 70 mg/kg of fibrinogen concentrate and achieved a target level of fibrinogen expected to prevent bleeding.

TOPICAL HEMOSTATIC AGENTS

Topical hemostatic agents are used extensively by orthopedic, neuro, cardiac, and vascular surgeons to promote hemostasis locally at the site of surgery.
and vascular. These agents can be classified based on their mechanism of action and include physical or mechanical agents, caustic agents, biologic physical agents, and physiologic agents. One of the widely used agents is topical thrombin.71 Bovine-derived thrombin until recently was the only topical thrombin available, and has the potential to induce immune responses following human exposure.71 There are now purified human thrombin (purified from multiple donors) and a recombinant thrombin for RECOTHROM™.

**THE FUTURE**

The potential for bleeding in a perioperative setting represents a growing problem for clinicians. The increasing use of anticoagulation agents creates a need for multiple pharmacologic approaches. The growing use of clopidogrel, the new agent prasugrel, and newer anticoagulants will continue to pose new paradigms and potential problems in managing surgical patients. Newer therapies including recombinant therapies provide clinicians with the ability to give key coagulation proteins to treat hemorrhage when standard therapies are ineffective.

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