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Managing Hemostasis in an Era of Conventional and Novel Anticoagulants

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Introduction

A new era offers increased choices in anticoagulant therapy. The list of anticoagulants used in the United States is growing, with several agents recently approved in the last decade and numerous others awaiting approval. Cardiothoracic anesthesiologist Jerrold H. Levy offers insights on both conventional and novel anticoagulants and the challenges they pose for clinicians, who must manage the hemostatic stability of their patients in emergent situations or when urgent invasive procedures are required.

Background

Anticoagulants have been a component of the US drug armamentarium for more than 70 years, with the approval of heparin for commercial use in 1937. A rapidly growing elderly population will likely increase the need for anticoagulants. According to US Census data, the number of persons aged 65 years and older will more than double by the middle of this century, to 80 million, and the oldest old (persons aged 85 years and older) are projected to be the fastest growing segment into the 21st century.¹ Older Americans also take more medications than any other segment of the US population, consuming an average of 30% of all prescription drugs,^{2,3} many for health problems such as stroke and atrial fibrillation (AF),⁴ conditions targeted by anticoagulants.

For many years, heparins and warfarin were the only anticoagulants available. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have established efficacy for the prevention of venous thromboembolism (VTE) and initial treatment of arterial or venous thromboembolism.⁵ However, with heparin use, platelet count needs to be monitored regularly because of the risk for heparin-induced thrombocytopenia.⁵ Warfarin, the only oral anticoagulant currently available in the United States, is effective for patients with a variety of conditions, including VTE, AF, and mechanical prosthetic heart valves.⁶ However, the agent has multiple limitations that include narrow therapeutic windows, unpredictable pharmacokinetics and

pharmacodynamics, delayed onset of action, drug and dietary interactions, and need for frequent monitoring.⁵⁻⁷ Warfarin, like all anticoagulants, is also associated with bleeding risk,^{6,8} increasing the risk of major bleeding by 0.5% per year and the risk of intracranial hemorrhage by approximately 0.2% per year, according to one report.⁸ In another report, among elderly patients with AF on warfarin therapy, the rate of major hemorrhage was calculated to be 7.2 per 100 person-years and the rate of intracranial hemorrhage was 2.5%.⁴

Despite the limitations of conventional anticoagulants, it was not until the 21st century that newer agents entered the market (**Table 1**). In the interim between 1916, when heparin was first discovered, and the present, a greater understanding of the coagulation system occurred, spurring efforts to develop novel agents that were more predictable, easier to administer, had minimal drug and food interactions, did not require monitoring, and posed a lower bleeding risk.^{6,9}

Table 1. Conventional and novel anticoagulants approved or in development in the United States

| | |
|---------------------|---|
| Heparin | <ul style="list-style-type: none"> • 1916, discovery • 1935, enters clinical trials • 1937, approved for use in US • 1940s, unfractionated heparin commercially available in US • 1990, LMWH commercially available in US |
| Warfarin | <ul style="list-style-type: none"> • 1954, approved by FDA |
| Fondaparinux | <ul style="list-style-type: none"> • 2001, approved by FDA for prophylaxis of DVT in orthopedic patients |
| Idraparinux | <ul style="list-style-type: none"> • 2009, FDA approval sought for PE and DVT indications • 2011, FDA approval sought for stroke prevention in AF patients |
| Rivaroxaban | <ul style="list-style-type: none"> • September 2008, approval from Health Canada for prevention of VTE in THR or TKR • September 2008, European Commission approves for VTE prevention in adult patients undergoing elective HR or KR • March 19, 2009, FDA advisory panel recommends approval for patients undergoing HR or KR • FDA approval expected in 2009 |
| Argatroban | <ul style="list-style-type: none"> • June 30, 2000, FDA approval for prophylaxis or treatment of thrombosis in patients with HIT • April 9, 2002, new indication approved for patients at risk for HIT who are undergoing PCI |
| Dabigatran | <ul style="list-style-type: none"> • 2007, approval of European Commission for prophylaxis after THR or TKR • 2010, FDA approval expected for adults undergoing elective THR or TKR |

LMWH=low-molecular-weight heparin; FDA=Food and Drug Administration; DVT=deep vein thrombosis; PE=pulmonary embolism; AF=atrial fibrillation; VTE=venous thromboembolism; THR=total hip replacement; TKR=total knee replacement; HIT=heparin-induced thrombocytopenia; PCI=percutaneous coronary intervention.

Several anticoagulants recently have been approved and several others are in the pipeline awaiting approval. Argatroban and fondaparinux were introduced approximately 10 years ago for prophylaxis of deep vein

thrombosis (DVT) and prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT) and those patients at risk for HIT, respectively. Other agents, including apixiban, dabigatran, idraparinux, and rivaroxaban, are approved in some countries. An advisory panel recently recommended that the US Food and Drug Administration (FDA) approve the investigational factor Xa inhibitor rivaroxaban.¹⁰

Whereas conventional anticoagulants may act on several coagulation factors, the newer agents provide selective inhibition of specific aspects of the coagulation cascade (see **Figure 1**).¹¹ These newer agents include direct thrombin inhibitors and factor Xa inhibitors. Although novel anticoagulants differ from conventional agents in the key enzymes they target in the coagulation cascade, they all have a potential risk for bleeding complications.¹¹⁻¹⁶ Moreover, there are no specific antidotes for the newer anticoagulants to reverse bleeding in emergent situations or when invasive procedures are required,^{5,8,17,18} although some interventions show promise, based on anecdotal reports and small-scale studies.^{8,11,12,19} This combination of bleeding risk and lack of an established antidote poses a challenge for clinicians, who must manage the hemostatic stability of their patients in an era of conventional and novel anticoagulants.

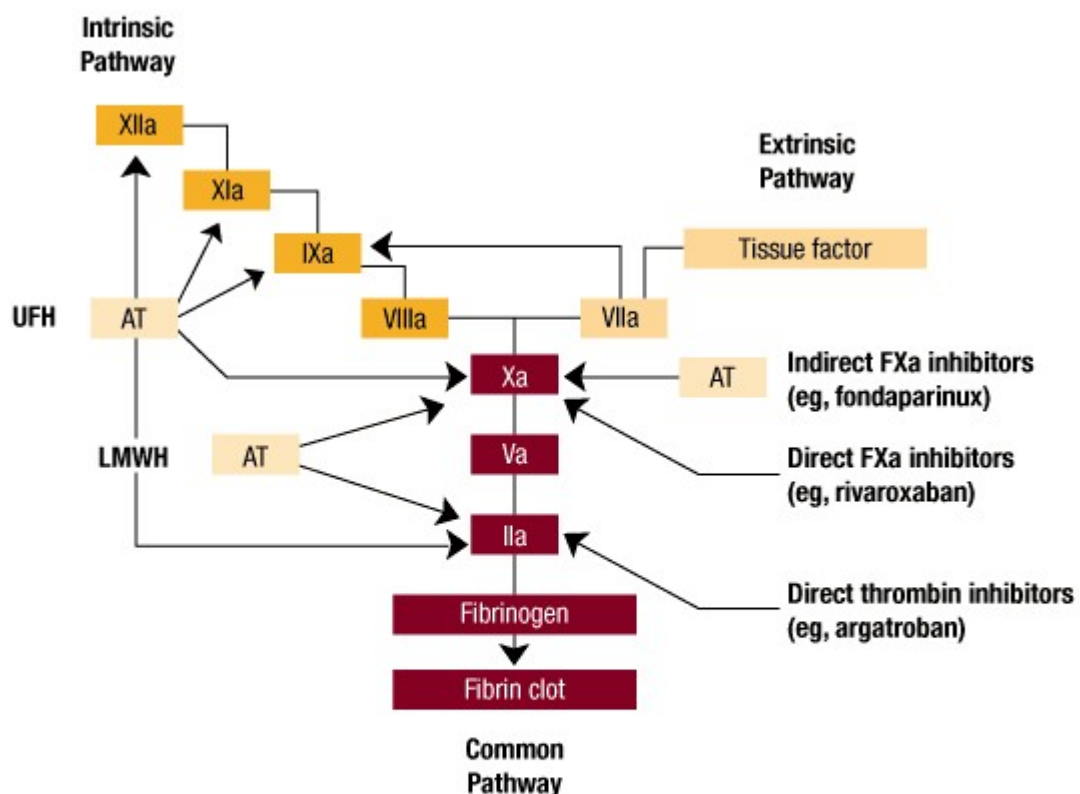


Figure 1

Mechanisms of action of antithrombotic agents, other than warfarin, in the clotting cascade.
Posted with permission from Gulseth MP, et al.¹¹

Reversal of Anticoagulant Therapy

The balance of bleeding and clotting is integral to hemostatic stability. This principle is especially important in the management of patients on anticoagulant therapy. Such therapy places patients at risk for bleeding, yet

without therapy, the risk for thromboembolic complications due to the precipitating condition becomes a real possibility.⁸ Appropriate management for patients on anticoagulant therapy who need emergency surgery or an urgent invasive procedure usually entails rapid reversal of treatment. Each clinical situation requires an assessment of the benefits and risks of reversal and consideration of potential strategies.⁸

For the most part, treatment strategies are in place for conventional anticoagulants—unfractionated heparin and warfarin—but for LMWH and the newer agents, no definitive strategy has yet to be indentified that reverses the effects of bleeding.⁸ **Table 2** provides a list of commonly used anticoagulants and agents for their reversal.

| Table 2. Commonly used anticoagulants and their antidotes | | | |
|--|---|--|---|
| | Time until restoration of hemostasis after cessation of therapeutic dose | Antidote | Remark |
| Heparin | 3-4 h | Protamine sulphate 25-30 mg; immediate reversal | One milligram of protamine per 100 anti-Xa units given in the last 2-3 h |
| LMW heparin | 12-24 h | (Partially) protamine sulphate 25-50 mg; immediate reversal | One milligram of protamine per 100 anti-Xa units given in the last 8 h |
| Pentasaccharides | Fondaparinux 24-30 h Idraparinux 5-15 days | Recombinant factor VIIa 90 ug/kg (?); immediate thrombin generation | Based on laboratory end points; no systematic experience in bleeding patients |
| Vitamin K antagonists | Acenocoumarol 18-24 h Warfarin 60-80 h Phenprocoumon 8-10 days | Vitamin K IV: reversal in 12-16 h Vitamin K orally: reversal in 24 h PCC: immediate reversal | Dose of vitamin K or PCCs dependent of INR and body weight |
| Oral thrombin and factor Xa inhibitors | Dependent of compound, usually within 12 h | Recombinant factor Xa for Xa inhibitors, unsure for IIa inhibitors | Based on laboratory end points; no systematic experience in bleeding patients |

Adapted from Levi M.⁹

Heparin

Protamine is effective for neutralizing the anticoagulant effects of heparin but not LMWH.^{8,20} Because heparin has a short half-life, anticoagulant effects are eliminated within 3 to 4 hours of terminating continuous IV administration, in which case no further action likely is required for reversal. However, if immediate neutralization of the agent is required, IV protamine is the appropriate antidote.⁸ Methods for counteracting the effects of LMWH need better elucidating.⁸

Warfarin

The anticoagulant effects of warfarin may be reversed over time with administration of vitamin K and acute use of prothrombin complex concentrates (PCC).^{8,21-26} Although vitamin K is an acceptable method of reversal, it takes several hours to achieve clinical effect.²² Vitamin K-dependent factors also can be administered using fresh frozen plasma (FFP), the only agent currently available in the United States, but large volumes necessary to provide factor replacement may result in circulatory overload and are a leading cause of transfusion-related acute lung injury (TRALI).^{8,27}

More rapid reversal of warfarin may be achieved with administration of PCC.^{25,26} In a small-scale dosing study, Junagade et al documented the successful use of PCC in 21 patients for whom immediate reversal of warfarin was necessary.²¹ For this group of patients, the researchers observed that a dose of 500 to 1000 IU of PCC was adequate to achieve reversal; however, the size of the study population was an obvious limitation, and further studies are warranted to determine appropriate dosing for reversal.

Anecdotal reports and case studies demonstrate the efficacy of off-label use of recombinant factor VIIa (rVIIa) for the emergency reversal of anticoagulation with heparins or warfarin. Ingerslev and colleagues conducted a database review of patients receiving rVIIa for reversal of LMWH, UFH, coumarin, or warfarin. Of 18 patients identified, 10 had cessation of bleeding following administration of rVIIa; bleeding was markedly decreased in 5 other patients and slowed considerably in 3 patients.²² Three-quarters of all patients (12/16) experienced improved hemostasis within 2 hours of receiving the first dose of rVIIa.²²

Taketomi and colleagues report less favorable outcomes with rVIIa administered as a reversal agent. Researchers used thrombelastography to compare the efficacy of PCC versus rVIIa in reversing the anticoagulant effects of warfarin and concluded that PCC was superior in restoring overall thrombin generation.²⁸

In an uncontrolled case series, Deveras et al evaluated the efficacy and safety of rVIIa in 13 patients who required rapid warfarin reversal.²³ Prothrombin time (PT) and international normalized ratio (INR) were measured before and after administration of rVIIa, and in all patients, INR was reduced after a single infusion of the agent.²³

Fondaparinux and Idraparinux

Fondaparinux and idraparinux are pentasaccharides that bind and potentiate antithrombin to block factor Xa. While fondaparinux has been commercially available in the United States for nearly 10 years, idraparinux is currently under investigation (see Table 1). Both agents have a relatively long half-life, approximately 20 hours for fondaparinux and 5½ days for idraparinux.⁸ This necessitates having a suitable antidote available should major bleeding events occur or if invasive surgical interventions are required. To date, rVIIa has been the only agent evaluated in detail to reverse the anticoagulant effect of pentasaccharides.⁸ Two randomized controlled trials conducted by Bijsterveld and colleagues demonstrated that rVIIa may be useful in reversing the anticoagulant effects of fondaparinux or idraparinux.^{12,19}

In the first trial, the ability of rVIIa to reverse the effect of fondaparinux was evaluated in 16 healthy male subjects, divided into 1 of 3 treatment groups. Each group received either a single SC dose of fondaparinux plus single IV bolus of rVIIa, fondaparinux plus placebo, or placebo plus rVIIa.¹² Researchers observed that rVIIa normalized coagulation times and thrombin generation during fondaparinux treatment. Normalization was maintained for up to 6 hours after rVIIa injection.¹²

In a separate study, Bijsterveld and colleagues examined whether rVIIa could neutralize the anticoagulant effects of idraparinux.¹⁹ Like their previous trial with fondaparinux, this was a small-scale study. Twelve healthy males received SC idraparinux and were subsequently randomized to 1 of 2 treatment regimens: rVIIa 3 hours after idraparinux and placebo 171 hours after idraparinux or placebo 3 hours after idraparinux and rVIIa 171 hours after idraparinux.¹⁹ Researchers found that rVIIa significantly decreased the inhibitory effect of idraparinux on thrombin generation (P=.001) and clotting times, including activated partial thromboplastin time (aPTT) (P=.002) and PT (P=.004), in healthy subjects.¹⁹

Argatroban and Dabigatran

Direct thrombin inhibitors argatroban and dabigatran bind directly to thrombin and block its interaction with substrates. Argatroban has been approved in the United States for the treatment of heparin-induced thrombocytopenia. Dabigatran is under evaluation in late-stage trials in the United States for VTE following orthopedic surgery. No antidote has been identified for the reversal of their anticoagulant effects, but these agents have a relatively short half-life, and anticoagulant effects subside within 12 to 24 hours following the last dose.²⁹

Rivaroxaban

Based on promising results of late-stage trials,^{13,15} the factor Xa inhibitor rivaroxaban has been recommended for approval by an FDA advisory panel for prevention of thrombotic events in hip and knee replacement surgery.¹⁰ However, like other newer anticoagulants, managing bleeding events in patients receiving this medication is not clear.⁸ It has been speculated that rVIIa and PCC may reverse the effects of high-dose rivaroxaban,¹⁷ but there is no direct proof to date.

Monitoring Anticoagulant Therapy

Although it would be beneficial to accurately monitor the reversal of anticoagulants during acute bleeding or prior to invasive procedures, currently available tests all have potential limitations. The aPTT is not useful as a monitoring assay for LMWH and cannot be used for monitoring the neutralizing effect of protamine.⁸ The anti-Xa assay, the most commonly used assay for direct measurement of heparin activity, cannot predict bleeding.³⁰ PCC and rVIIa, therapies used as reversal agents, are inconsistent in their action on INR and aPTT,²² and there is no correlation between PT and factor VII activity levels.²³

Some researchers, however, are trying to develop an accurate global assay. Recently, Gatt and colleagues examined the ability of the calibrated automated thrombin (CAT) generation test versus the aPTT and anti-Xa assay to detect reversibility of heparinoids by various antidotes, including protamine, factor VIII inhibitor bypassing activity (FEIBA), rVIIa, and FFP. Following extensive testing, the researchers found the CAT to be superior to traditional coagulation tests in monitoring the efficacy of reversal agents on anticoagulants.³⁰

Conclusion

For years, heparin and warfarin have been the mainstay of anticoagulant therapy, despite limitations associated with their use. Within the past decade, a number of anticoagulants either have been approved or are in development, expanding the potential anticoagulant treatment options. Nevertheless, as these novel agents usher in a new era of anticoagulant therapy, the need remains for reliable antidotes, especially in urgent and emergent bleeding situations, and accurate monitoring so clinicians may optimize hemostatic outcomes in their patients.

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