A pharmacologic overview of current and emerging anticoagulants

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■ ABSTRACT

For over 50 years, anticoagulant options for the treatment and prevention of thrombosis have been limited mainly to traditional agents such as unfractionated heparin and oral vitamin K antagonists such as warfarin. These traditional agents are fraught with limitations that complicate their clinical use. A variety of novel anticoagulants with improved pharmacologic and clinical profiles have recently been introduced or are in development, offering benefits over traditional therapies. Specifically, progress has been made in the development of low-molecular-weight heparins, factor Xa inhibitors, and direct thrombin inhibitors. Because of their convenience and ease of use, some of these novel compounds are competing with the traditional anticoagulants and are needed additions to the antithrombotic arsenal.

Anticoagulant therapy has historically consisted of heparins for the treatment of acute thrombosis and vitamin K antagonists for long-term or chronic treatment.[1] Though effective if appropriately dosed and monitored, these traditional agents have shortcomings that stem mainly from their nonspecific mechanisms of action and variable pharmacodynamics. This has left a persisting need for novel anticoagulants that have more specific and targeted action and are easier to administer and manage.[2] Recent efforts have focused on the development of more specific agents that may offer benefits over traditional anticoagulants. As a result, today there are four major classes of anticoagulants available in the United States for the prevention and treatment of thrombosis:

- Vitamin K antagonists such as warfarin
- Indirect thrombin inhibitors such as unfractionated heparin and low-molecular-weight heparins
- Direct thrombin inhibitors
- Factor Xa inhibitors.

This article reviews and compares pharmacologic characteristics among these various traditional and novel anticoagulants. These agents' modes of action are depicted in **Figure 1** and their clinical and pharmacologic profiles are outlined in **Table 1**.

■ VITAMIN K ANTAGONISTS

The first vitamin K antagonists (VKAs), or coumarin derivatives, were developed in the early 1940s, and the first clinical trials began in 1954. Sweet clover disease, a malady in which cattle died of hemorrhagic complications after ingesting spoiled sweet clover, led to the discovery of dicumarol and its congener warfarin by Dr. Karl Paul Link in 1940. For the last 50 years VKAs have been the mainstay oral anticoagulants in North America.

Two classes of VKAs have been approved by the US Food and Drug Administration (FDA), the coumarins and the indandiones. One drug from each class, warfarin and anisindione, is available in the United States, but warfarin is by far the most commonly used oral agent. Warfarin is the anticoagulant of choice when long-term or extended anticoagulation is indicated.

The VKAs' efficacy has been demonstrated for the primary and secondary prevention of venous thromboembolism (VTE), prevention of systemic VTE in patients with atrial fibrillation or prosthetic heart valves, prevention of thromboembolic stroke, and primary and secondary prevention of acute myocardial infarction.[3]

Warfarin exerts its anticoagulant effect by inhibiting activation of the vitamin K–dependent clotting factors II, VII, IX, and X as well as the anticoagulant proteins C and S. The degree of depression of clotting factors is dose-dependent, with a decrease in each factor of approximately 30% to 50% at therapeutic doses.

When warfarin therapy is initiated, attainment of complete antithrombotic effect is usually delayed for several days, owing to the various half-lives of the clotting factors (6 to 72 hours). Proteins C and S are inhibited more rapidly because of their shorter half-lives, which may potentially lead to a "paradoxical" procoagulant state during the first few days of therapy. It is therefore crucial that patients with acute thrombosis receive a parenteral anticoagulant (heparin or low-molecular-weight heparin) while transitioning to therapeutic doses of warfarin.[3,4]

Why alternatives are needed

Although warfarin is effective, its use is limited by various challenges:

- The need for frequent monitoring of anticoagulant effect via the international normalized ratio
- Large interindividual dosing differences
- A narrow therapeutic index
- Slow onset and offset of action
- Interactions with dietary vitamin K and many other medications, vitamins, and herbal supplements
- Drug-disease interactions
- Genetic variations in anticoagulant response
- The need for constant dose adjustments, patient education, strict compliance, and frequent follow-up.[2,3,5]

These limitations render VKAs cumbersome for day-to-day clinical use and cumbersome for patients, underscoring the need for novel oral agents that are more convenient and less complex to use.

■ HEPARINS: UNFRACTIONATED AND FRACTIONATED

Discovered in the early 20th century, unfractionated heparin (UFH) is commercially isolated from porcine or bovine mucosa. Heparin exerts its anticoagulant effect via a plasma cofactor, antithrombin, inhibiting thrombin (factor IIa) and factor Xa in an equal (1:1) ratio. It binds nonspecifically to a number of plasma and cellular proteins, resulting in decreased bioavailability and substantial interpatient variability in anticoagulant response. Thus, when given at therapeutic doses, UFH requires frequent laboratory monitoring to assess the level of anticoagulation, as measured by the activated partial thromboplastin time (aPTT).[6]

Fractionated or low-molecular-weight heparins (LMWHs) are derived by chemical or enzymatic depolymerization of UFH, resulting in shorter heparin chains that have an enhanced affinity for inhibiting factor Xa relative to their activity against thrombin. The factor Xa:IIa ratios for LMWHs are agent-specific and range from 4:1 to 2:1. Three LMWHs are currently available in the United States: dalteparin, enoxaparin, and tinzaparin.[6,7]
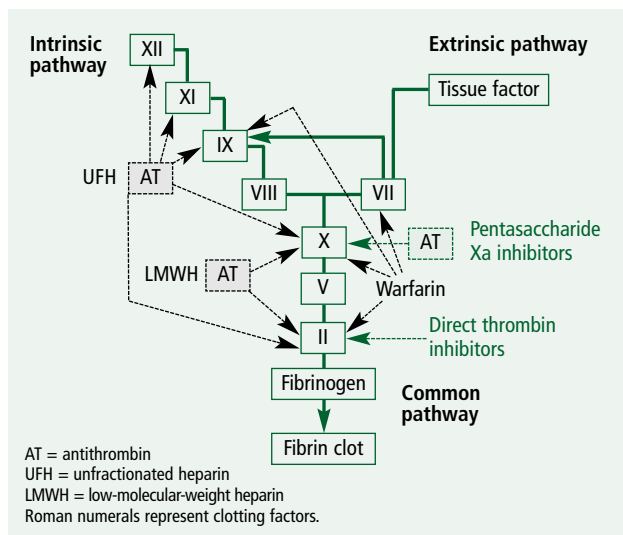
FIGURE 1. The pathways of coagulation and the modes of action of various anticoagulant classes. The coagulation cascade comprises two independent pathways—intrinsic and extrinsic—that converge on the activation of factor X and initiate the common pathway that leads to thrombin generation and fibrin formation.

Advantages of LMWHs

LMWHs have substantially improved pharmacodynamic and pharmacokinetic properties as compared with UFH. They exhibit less binding to plasma and cellular proteins, resulting in a more predictable anticoagulant response. Consequently, routine monitoring of anticoagulation intensity and dose adjustment are not required in most patients. LMWHs also have longer plasma half-lives, allowing once- or twice-daily administration (vs twice or thrice daily with UFH), improved subcutaneous bioavailability, and dose-independent renal clearance. Because of their ease of use, LMWHs can be given more readily on an outpatient basis, providing patients a more convenient and less complex form of therapy. LMWHs also have a more favorable side-effect profile than does UFH, including a lower incidence of heparin-induced thrombocytopenia (HIT) and osteopenia. However, LMWHs cross-react with UFH and should not be given as alternative anticoagulants in patients with documented HIT.[8,9]

Other factors to consider

Additional factors to weigh when considering LMWHs relative to UFH are their higher acquisition costs; the more limited data on their use in high-risk populations such as obese patients, pregnant women, and pediatric patients; and the fact that they, unlike UFH, are only partially reversible with protamine. In addition, LMWHs require dose adjustment in patients with renal impairment, owing to their renal elimination.[10,11]

TABLE 1
Pharmacologic and clinical profiles of anticoagulant agents

Characteristic	Warfarin	Unfractionated heparin	Low-molecular-weight heparins	Factor Xa inhibitors	Direct thrombin inhibitors
No. of targets in coagulation cascade, specificity of activity	Multiple, nonspecific	Multiple, nonspecific	Relatively few and specific	Few, specific	Few, specific
No. of times dosed daily	1	2–3*	1–2	1	1–2*
Route of administration	Oral	IV or SC	SC	SC or oral	IV, SC, or oral
Laboratory monitoring requirements	INR	aPTT, platelet count	Platelet count; anti-Xa monitoring in special groups	None	Varies[†]
Variability in response	High	High	Relatively low	None	Relatively low
Risk of thrombocytopenia	None	2%–5%	1%–2%	None	None

*Or continuous infusion (for select indications)
[†]aPTT for parenteral agents; liver function testing for argatroban and possibly for oral agents
aPTT = activated partial thromboplastin time; INR = international normalized ratio; IV = intravenous; SC = subcutaneous

Because of their quick onset of action, UFH and LMWHs are the anticoagulants of choice when a rapid anticoagulant effect is required. Both types of heparins are used for treatment of venous thrombosis and acute myocardial ischemia in higher "therapeutic" doses, as well as for VTE prevention in lower "prophylactic" doses. Even though UFH was the gold standard for anticoagulation for more than 60 years, its role is now challenged by the LMWHs, which have demonstrated at least comparable safety and efficacy, an improved side-effect profile, and more convenient dosing. Based on recently published and ongoing clinical trials, LMWHs are competing with UFH in all therapeutic and surgical interventions requiring anticoagulation.[1,6,12–14]

■ FACTOR Xa INHIBITORS

The factor Xa inhibitors are a novel class of anticoagulants; the first such agent was approved by the FDA in late 2001. They are synthetic versions of the five-sugar sequence of heparin and are thus referred to as pentasaccharides. Because of their very small molecular size, they exert their inhibitory activity specifically on activated factor X (Xa) and, unlike heparins, have no direct effect on factor IIa.[15,16]

Pentasaccharides can inhibit factor Xa directly or indirectly. The direct inhibitors bind to factor Xa without a cofactor, thus blocking its activity. Direct factor Xa inhibitors currently in development include tick anticoagulant peptide, YM-60828, and DX-9065a. The indirect inhibitors bind to antithrombin with high affinity, causing a permanent conformational change in antithrombin and increasing its rate of factor Xa inhibition. Because they are selective for factor Xa, they reduce thrombin generation without affecting circulating thrombin. Fondaparinux is the only member of the class that is commercially available in the United States. Additional agents such as idraparinux and razaxaban (formerly DPC-906) are undergoing clinical trials. Fondaparinux and idraparinux are given subcutaneously, whereas razaxaban is an oral formulation.[17–20]

As synthetic compounds, factor Xa inhibitors offer several advantages: no risk of animal pathogen transmission, batch-to-batch consistency, and unlimited sourcing. Other favorable attributes include a predictable and linear dose-response relationship, a quick time to maximum concentration, and a long half-life. Because of their predictable anticoagulant effect, factor Xa inhibitors, like LMWHs, do not require routine coagulation monitoring or dose adjustment. Fondaparinux has a half-life of 17 to 21 hours, allowing once-daily dosing, and idraparinux (an extended-release formulation) is being developed for administration as a once-weekly injection. Neither fondaparinux nor idraparinux is metabolized in the liver, so each has few drug interactions. Unlike the heparins, factor Xa inhibitors do not affect platelet function and do not react with heparin–platelet factor 4 (PF4) antibodies, thus reducing the risk of HIT. There has been no in vitro cross-reactivity with fondaparinux and antibodies to the heparin–PF4 complex, suggesting that this agent might be useful for treatment of patients with HIT and for prophylaxis in patients with a history of HIT.[19–22]

Fondaparinux is indicated for prophylaxis of venous thrombosis in patients undergoing hip replacement surgery, knee replacement surgery, and hip fracture surgery (including extended prophylaxis after hip fracture surgery). It also recently gained FDA approval for treatment of acute deep vein thrombosis and pulmonary embolism.[17] Idraparinux is being investigated for the treatment of VTE and for stroke prevention in patients with atrial fibrillation.

While a once-weekly agent such as idraparinux

would improve convenience and perhaps patient compliance, a potential drawback of these long-acting anticoagulants is that there is no antidote if the patient bleeds or requires an invasive procedure.[22,23] Clinically significant bleeding would require fresh frozen plasma and, potentially, red blood cell replacement. In the case of a life-threatening bleeding episode, one potential option to minimize bleeding is the use of recombinant factor VIIa, although this is very costly and can also increase the risk of thrombosis.[23]

In addition, since factor Xa inhibitors are renally eliminated, accumulation can occur in patients with renal dysfunction if there is not appropriate dose adjustment. Because of a current lack of specific dosing guidelines in special populations, fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) and in orthopedic surgery patients weighing less than 50 kg.[24]

Nonetheless, because of their convenience of use, factor Xa inhibitors are a welcome addition to the more traditional anticoagulants for the treatment and prevention of VTE.[17,21,24]

■ DIRECT THROMBIN INHIBITORS

Because thrombin is the central effector of coagulation and amplifies its own production, it is a natural target for direct pharmacologic intervention. Direct thrombin inhibitors (DTIs) bind with thrombin to prevent an interaction between the enzyme and substrates. Several parenteral DTIs are approved for use in the United States, including lepirudin, bivalirudin, argatroban, and desirudin.[25,26]

The advantages of DTIs include a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of plasma protein and platelet interactions that can lead to complications such as HIT. Unlike heparins, DTIs do not require antithrombin as a cofactor and do not bind to plasma proteins. Therefore, they produce a more predictable anticoagulant effect, and variability of patient response is low relative to other drug classes.[25,26]

Lepirudin has a short half-life—approximately 80 minutes following intravenous administration. Its elimination is primarily renal, so dosing must be adjusted according to the patient's renal function. The dose should be monitored and adjusted to an aPTT ratio of 1.5 to 2.5 because bleeding risk increases above this range without an increase in efficacy. Lepirudin is approved for use in patients with HIT and related thrombosis.[25–27]

Bivalirudin, a DTI with a smaller molecular weight, is also given intravenously. It has a shorter elimination half-life than lepirudin (≈25 min), and

its elimination is only partially renal. Patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min) may require dose adjustment and monitoring of anticoagulation status since clearance of bivalirudin is reduced by approximately 20% in these patients. The activated clotting time can be used to monitor bivalirudin's anticoagulant effect during percutaneous coronary intervention (PCI). Bivalirudin is approved for use in patients undergoing percutaneous transluminal coronary angioplasty.[25–27]

Argatroban, a small-molecule DTI, is also given intravenously. It has an elimination half-life of 40 to 50 minutes. Monitoring of the aPTT is required to assess its anticoagulant activity. Argatroban is hepatically metabolized, so dose reductions and careful monitoring are recommended in patients with hepatic dysfunction. Renal impairment has no influence on its elimination half-life and so does not require dose adjustment. Like the other DTIs, argatroban has no known antidote. Argatroban is approved for the prevention and treatment of thrombosis in patients with HIT and in patients with HIT undergoing PCI.[25–27]

Desirudin is the first subcutaneously administered DTI and also the first DTI approved for prevention of VTE after hip replacement surgery, but it is not yet commercially available in the United States. However, it is available in several European countries. Desirudin has an elimination half-life of 2 to 3 hours and is typically dosed every 12 hours. It is primarily eliminated and metabolized by the kidney, so dose reduction is needed in patients with renal impairment. The aPTT is the test used to measure desirudin's anticoagulant activity.[25]

The quest for oral DTIs

DTIs can be structurally modified for oral administration. Approximately 10 oral DTIs are reported to be in development, of which ximelagatran is the furthest along.

Ximelagatran is a small-molecule prodrug that is rapidly absorbed following oral administration and converted to melagatran, its active form, achieving peak plasma concentrations in 1.6 to 1.9 hours. Ximelagatran has several advantages compared with the mainstay oral anticoagulant, warfarin:
- A predictable dose response, requiring no dose adjustment or coagulation monitoring
- A wider therapeutic index
- A rapid onset and offset of effect
- An apparent lack of clinically significant interactions with drugs and foods metabolized via the CYP450 isoenzyme.[28,29]

Stable, fixed doses of ximelagatran without monitor-

ing of coagulation parameters have been successfully studied in large phase 3 trials in various clinical settings, including stroke prevention in patients with atrial fibrillation, VTE prevention after major joint replacement, acute VTE treatment and secondary prevention of VTE after idiopathic VTE, and secondary prevention of myocardial infarction.[30–32] While these studies indicate that the drug can potentially be used in these clinical settings, the FDA recently refused to approve ximelagatran over concerns about liver toxicity.

Specifically, ximelagatran is associated with a 6% to 10% increase in hepatic transaminase levels in the first 2 to 6 months of long-term therapy, which is likely to require intensive liver function monitoring. The true clinical significance of these findings remains unclear at this time. Also, melagatran is renally eliminated, so dose adjustment will be required in patients with renal impairment. Without laboratory indicators of coagula-

tion, getting the dose right is crucial. Finally, there is no known antidote for reversal of ximelagatran's effect, though it is much shorter-acting than warfarin.[32] Even with these hurdles, ximelagatran's advantages would most likely make its use attractive in clinical practice, as it is more convenient and less complicated to administer on a chronic basis than is warfarin.

■ SUMMARY

Novel anticoagulants have been developed to overcome the limitations of nonspecific traditional anticoagulants. They offer more specific activity on the coagulation cascade, predictable pharmacodynamics and pharmacokinetics, simpler dosing regimens, and few or no laboratory monitoring requirements. Some of these agents, such as factor Xa inhibitors and parenteral DTIs, are already available and are clearly improved additions to the antithrombotic arsenal.

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