

INTRODUCTION

Edith A. Nutescu, PharmD

Anticoagulant agents are mainstay therapies in the prevention and treatment of arterial and venous thrombosis. Available anticoagulants include the direct and indirect thrombin inhibitors (Table).¹ The direct thrombin inhibitors (DTIs; lepirudin, desirudin, bivalirudin, argatroban) exert their anticoagulant effect by sole inhibition of thrombin, whereas the indirect inhibitors (unfractionated heparin [UFH] and low molecular weight heparins [LMWH]) need a cofactor (antithrombin III) to exert their anticoagulant effect and block both thrombin and activated factor X (FXa) (Figure).^{1,2} The heparins (UFH and LMWH) exert their anticoagulant effect on fluid phase thrombin and FXa, and are resistant to clot-bound thrombin and clot-bound prothrombinase-associated FXa.³ Although UFH and the DTIs suppress existing thrombin activity, thrombin generation is largely unaffected.⁴

The benefit of UFH is accepted and well documented in the treatment of arterial and venous thrombosis; however, its use is fraught with many limitations. UFH is associated with variable anticoagulant effect, requires routine monitoring and dose adjustment, and carries the risk of heparin-induced thrombocytopenia.¹ The LMWH were developed to overcome some of the limitations of UFH. These agents have a higher affinity for inhibiting FXa compared with that of thrombin, and are less complex to use in the clinical setting compared with UFH.⁵ The more favorable benefit-risk profile (ie, better side-effect profile) of LMWH, with a higher affinity for FXa inhibition compared with UFH, has triggered interest in the search and development of more selective anticoagulant agents, such as the FXa inhibitors.⁶

As the penultimate enzyme in the coagulation cascade, FXa has a critical role by ultimately regulating thrombin production (Figure).¹ FXa converts prothrombin to

thrombin via the prothrombinase complex, leading to platelet activation and formation of the fibrin clot. FXa is generated via the intrinsic or extrinsic pathways, and 1 molecule of FXa can generate more than 1000 thrombin molecules. In addition, a massive burst of thrombin generation is caused by prothrombinase-bound FXa because its reaction rate is 300 000-fold higher compared with free FXa.^{6,7} The inhibition of thrombin generation by blocking FXa has been validated as an effective antithrombotic approach with the use of the highly selective, direct and indirect FXa inhibitors. The indirect FXa inhibitors (eg, fondaparinux) exert their effect via a cofactor (antithrombin III), whereas the direct inhibitors (eg, DX-9065a, otamixaban) block FXa directly.^{1,2,6,7}

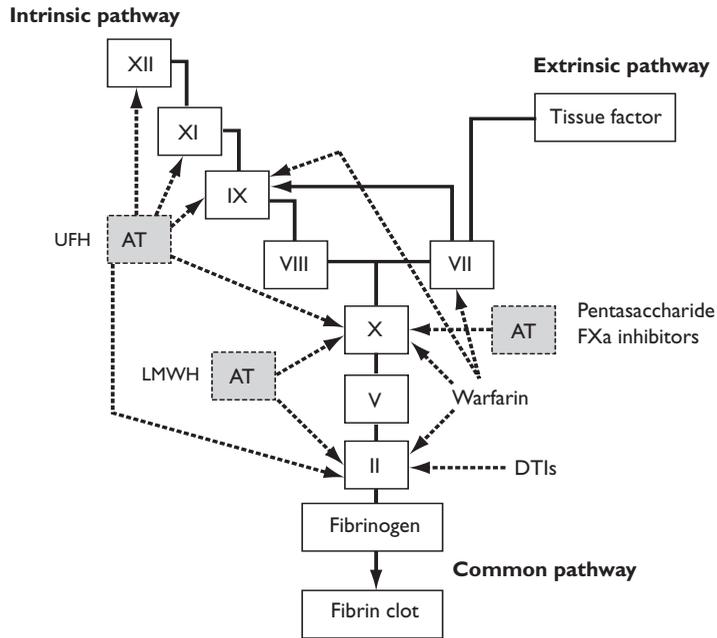
Ample clinical evidence now supports the role of the FXa inhibitors as anticoagulants and as effective therapeutic agents for the prevention and treatment of venous and arterial thrombosis. Fondaparinux, an indirect FXa inhibitor, has equivalent or greater efficacy than the LMWH enoxaparin in the prevention of venous thromboembolism (VTE) after orthopedic surgery,⁸ similar efficacy to dalteparin in prevention of VTE after abdominal surgery,⁹ better efficacy than placebo in prevention of VTE in medical patients,¹⁰ similar efficacy to enoxaparin and UFH in treatment of deep vein thrombosis and pulmonary embolism,^{11,12} and similar efficacy to UFH and enoxaparin in treatment of patients with acute coronary syndromes (ACS).^{13,14} In addition, in patients with ACS, there is a safety and mortality benefit in favor of fondaparinux compared with enoxaparin.¹⁴

Although these newer agents have higher acquisition costs than warfarin or UFH, their use has grown rapidly, making them among

Address correspondence to: Edith A. Nutescu, PharmD, Department of Pharmacy Practice, University of Illinois at Chicago, 833 S. Wood St., RM 164, MC886, Chicago, IL 60612. E-mail: enutescu@uic.edu.

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Figure. The Coagulation Cascade and Modes of Action of Anticoagulant Agents



The coagulation cascade comprises 2 independent pathways: intrinsic and extrinsic. These pathways converge at the activation of factor X and initiate the common pathway that leads to thrombin generation and fibrin formation. Roman numerals represent clotting factors. AT indicates antithrombin; UFH, unfractionated heparin; LMWH, low molecular weight heparin; FXa, factor Xa; DTI, direct thrombin inhibitor. Source: Adapted with permission from Reference 1.

the highest ranked drug classes in terms of hospital pharmaceutical expenditures.¹⁵ With the expansion in the number of anticoagulant agents and the indications for which they can be used, clinicians can be challenged by selecting the most appropriate agents, optimal dosing regimens, and the most cost-effective options. This supplement will review the medical and economic impact, new treatment options, and cost-effectiveness of novel therapies for ACS.

REFERENCES

1. Nutescu EA, Shapiro NL, Chevalier A, Amin AN. A pharmacologic overview of current and emerging anticoagulants. *Cleve Clin J Med.* 2005;72(suppl 1):S2-S6.
2. Bauer KA. New anticoagulants: anti IIa vs anti Xa—is one better? *J Thromb Thrombolysis.* 2006;21:67-72.
3. Petros S, Siegemund T, Siegemund A, Engelmann L. The effect of different anticoagulants on thrombin generation. *Blood Coagul Fibrinolysis.* 2006;17:131-137.
4. Nutescu EA, Shapiro NL, Chevalier A. New anticoagulant agents: direct thrombin inhibitors. *Clin Geriatr Med.* 2006;22:33-56.
5. Dinwoodey DL, Ansell JE. Heparins, low-molecular-weight heparins, and pentasaccharides. *Clin Geriatr Med.* 2006;22:1-15.
6. Ieko M, Tarumi T, Nakabayashi T, Yoshida M, Naito S, Koike T. Factor Xa inhibitors: new anti-thrombotic agents and their characteristics. *Front Biosci.* 2006;11:232-248.
7. Rajagopal V, Bhatt DL. Factor Xa inhibitors in acute coronary syndromes: moving from mythology to reality. *J Thromb Haemost.* 2005;3:436-438.

Table. Pharmacologic and Clinical Profiles of Anticoagulant Agents

Characteristic	Warfarin	UFH	LMWH	FXa Inhibitors	DTIs
No. of targets in cascade	Multiple	Multiple	Few	Few	Few
Specificity of activity	Nonspecific	Nonspecific	Specific	Specific	Specific
No. of daily doses	1	2-3*	1-2	1	1-2
Route	Oral	IV or SC	SC	SC, oral	IV, SC, oral
Laboratory monitoring	INR	aPTT, platelet count	Platelet count, anti-Xa in some patients	None	aPTT,* liver function†
Response variability	High	High	Low	None	Low
Risk of HIT	None	2%-5%	1%-2%	None	None

*Or continuous infusion for select indications.

†In some agents in this class.

UFH indicates unfractionated heparin; LMWH, low molecular weight heparin; FXa, factor Xa; DTIs, direct thrombin inhibitors; IV, intravenous; SC, subcutaneous; INR, international normalized ratio; aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia.

Source: Adapted with permission from Reference 1.

8. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR; for the Steering Committees of the Pentasaccharide Orthopedic Prophylaxis Studies. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med.* 2002;162:1833-1840.

9. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M, on behalf of the PEGASUS Investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg.* 2005;92:1212-1220.

10. Cohen AT, Davidson BL, Gallus AS, et al; for the ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ.* 2006;332:325-329.

11. Büller HR, Davidson BL, Decousus H, et al; to the

Matisse Investigators. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med.* 2004;140:867-873.

12. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med.* 2003;349:1695-1702.

13. The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA.* 2006;295:1519-1530.

14. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med.* 2006;354:1464-1476.

15. Schumock GT, Nutescu EA, Walton SM, Arondekar BV, Lewis RK. Survey of hospital policies regarding low-molecular-weight heparins. *Am J Health Syst Pharm.* 2002;59:534-538.