

LOW MOLECULAR WEIGHT HEPARIN AND FONDAPARINUX

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INTRODUCTION

The low molecular weight heparins (LMWHs) and the synthetic pentasaccharide, fondaparinux, offer several advantages over unfractionated heparin (UFH). Enoxaparin and dalteparin were approved in the United States in 1993 and 1994, respectively, followed by fondaparinux in 2001. Tinzaparin was approved and available in 2000, but was subsequently withdrawn from the market in 2011. These injectables have been traditionally used as prophylaxis for venous thromboembolism or as a bridge therapy to therapeutic oral anticoagulation. Based on their relative ease of dosing and monitoring, these agents frequently replace UFH in many clinical situations. This chapter will focus on those agents currently available in the United States, including enoxaparin, dalteparin, and fondaparinux.

PHARMACOLOGY AND PHARMACOKINETICS¹⁻⁹

Traditionally, unfractionated heparin was the parenteral anticoagulant used in the inpatient setting. Active unfractionated heparin compounds are composed of an inconsistent number of sugars, each ending in a specific pentasaccharide sequence. Using a consistent and shorter sequence of sugars improved the variability in the anticoagulant effect, giving rise to fractionated LMWH products.

Mechanism of Action

- LMWHs and fondaparinux are indirect inhibitors of clotting factors requiring antithrombin to exert an anticoagulant effect (**Figure 4-1**).
- A specific pentasaccharide sequence binds to antithrombin to potentiate its activity.
- LMWHs inhibit both Factor Xa and IIa (thrombin) activity.
- Fondaparinux selectively inhibits only Factor Xa.
- Refer to **Tables 4-1** and **4-2** for comparison of the specific clotting factors inhibited.

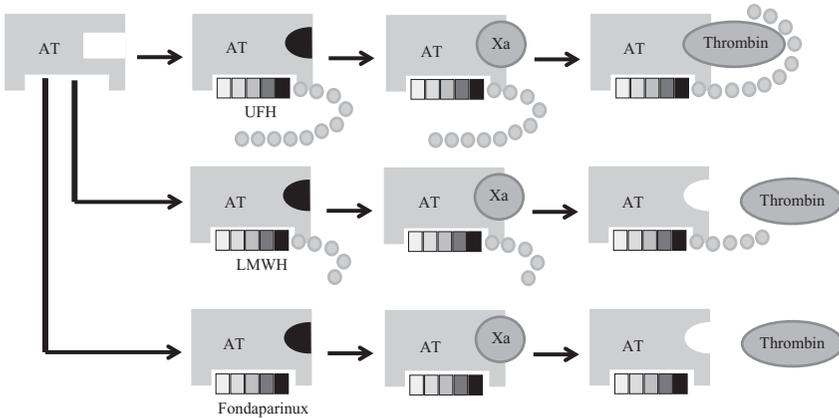


FIGURE 4-1. Mechanism of Action for LMWH and Fondaparinux in Comparison to UFH

AT: antithrombin, LMWH: low molecular weight heparin, UFH: unfractionated heparin

Source: Adapted from Weitz J. Low molecular weight heparins. *N Engl J Med.* 1997;337:688–698. Copyright ©1997 Massachusetts Medical Society. Used with permission from Massachusetts Medical Society.

TABLE 4-1: Commercially Available Agents in the United States

Drug	Therapeutic Class	Generic Version Available	Product Source	Clotting Factors Inhibited
Dalteparin (Fragmin)	LMWH	No	Chemical or enzymatic depolymerization of UFH	Xa>IIa
Enoxaparin (Lovenox)	LMWH	Yes	Chemical or enzymatic depolymerization of UFH	Xa>IIa
Fondaparinux (Arixtra)	Pentasaccharide	Yes	Chemical synthesis	Xa

LMWH: low molecular weight heparin, UFH: unfractionated heparin