

# Differentiation of the Low-Molecular-Weight Heparins

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The three low-molecular-weight heparins (LMWHs) available in the United States have been extensively evaluated for a wide array of indications. Properties associated with one LMWH cannot be assumed to be the same as those associated with another LMWH, as they are different pharmacologic entities. Therefore, therapeutic interchange of these agents is inappropriate. The pharmacokinetic and pharmacodynamic differences among LMWHs can be explained by comparing methods of preparation, molecular structures, half-lives, antithrombin- and non-antithrombin-mediated actions, effect on thrombus, and dosing interval. The Food and Drug Administration-approved indications and their respective levels of clinical evidence further differentiate these agents. A dichotomy in the results of clinical trials has been observed with the LMWHs. As the LMWHs are distinct compounds that each possess unique pharmacokinetic and pharmacodynamic profiles, treatment decisions should be based on the available safety and efficacy data for each LMWH. Agents should be prescribed only for those indications for which they have been shown to be effective and only at dosages that have been studied.

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Low-molecular-weight heparins (LMWHs) are heterogeneous mixtures of sulfated glycosaminoglycans with approximately one-third the molecular weight of unfractionated heparin (UFH).<sup>1</sup> They have several therapeutic advantages relative to UFH: a more predictable anticoagulation dose-response, improved subcutaneous bioavailability, dose-independent clearance, longer biologic half-life, lower frequency of thrombocytopenia, and a reduced requirement for routine laboratory monitoring.<sup>1, 2</sup> Although all the LMWHs share a similar mechanism of action, their molecular weight distributions vary, resulting in differences in their activity against factor Xa and thrombin, their affinity for plasma proteins (Table 1), and their plasma half-lives.<sup>2</sup>

Low-molecular-weight heparins have been

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evaluated extensively as treatment for a wide array of indications such as acute coronary syndromes, deep vein thrombosis (DVT), and pulmonary embolism (PE). They also have been studied for prevention of venous thromboembolism in several high-risk populations. Three LMWHs—dalteparin, enoxaparin, and tinzaparin—are available in the United States. Food and Drug Administration (FDA)-approved indications for these agents are product specific. Clinical evidence for various indications also differs. Nevertheless, many institutions claim that these agents are therapeutically equivalent and use them interchangeably.

In this article, dalteparin, enoxaparin, and tinzaparin are compared and contrasted to demonstrate that they are distinct pharmacologic entities and should not be interchanged. Pharmacokinetic and pharmacodynamic differences are recognized by comparing the following properties: method of preparation, molecular structure, half-lives, antithrombin- and non-antithrombin-mediated actions, effect on thrombus, and dosing interval. The FDA-

**Table 1. Biologic Consequences of Reduced Binding of LMWHs to Proteins and Cells<sup>1, 2</sup>**

Binding Target	Biologic Effects	Clinical Consequence
Thrombin	Reduced anti-IIa activity	None known
Proteins	Improved bioavailability, predictable anticoagulant response	Effective when given by subcutaneous injection, monitoring of anticoagulant effect usually unnecessary
Macrophages	Renally cleared	Longer plasma half-life, once-daily subcutaneous treatment effective
Platelets	Reduced frequency of heparin-antibodies	Reduced frequency of heparin-induced thrombocytopenia
Osteoblasts	Reduced activation of osteoblasts	Reduced frequency of osteopenia and osteoporosis

approval status and, most important, their respective available levels of clinical evidence, further differentiate these agents.

### Method of Preparation

Low-molecular-weight heparins are depolymerized porcine mucosal pharmaceutical grade heparin preparations, manufactured through distinct depolymerization processes (Table 2).<sup>3-6</sup> Nitrous acid depolymerization is used to produce dalteparin,<sup>3, 4</sup> and benzylolation followed by alkaline depolymerization is used in enoxaparin.<sup>3, 5</sup> Tinzaparin is made by enzymatic depolymerization with heparinase.<sup>3, 6</sup> The different depolymerization processes induce distinct changes to the heparin molecule, resulting in a unique molecular structure (Figure 1). Nitrous acid depolymerization induces the formation of anhydromannose (5-member ring) on the dalteparin molecule. In contrast, the processes used for enoxaparin and tinzaparin induce the introduction of a double bond at the end group.<sup>3-7</sup> In addition, each preparation is thought to have different proportions of antithrombin-binding regions as well as linkage regions, which are critical for their anticoagulant action.<sup>8</sup>

### Molecular Structure and Half-Life

The distinct manufacturing processes lead to the formation of a heterogeneous mixture of polysaccharide chains of different lengths and molecular weights (Table 3).<sup>1, 4-6, 9</sup> Of the three molecules, dalteparin has the largest mean molecular weight (6000 daltons), tinzaparin is somewhat smaller (4500 daltons), and enoxaparin is the smallest (4200 daltons).<sup>1</sup> In addition, their anti-Xa activities and half-lives

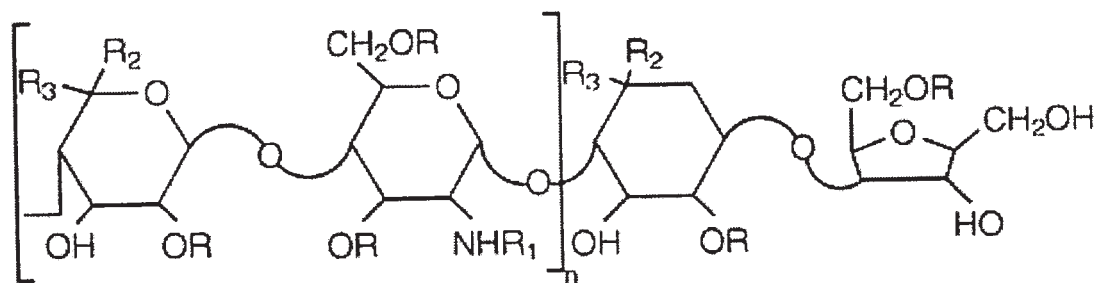
**Table 2. Methods of Preparation of FDA-Approved Low-Molecular-Weight Heparin Products<sup>3-6</sup>**

Agent	Method of Preparation
Dalteparin	Nitrous acid depolymerization
Enoxaparin	Benzylolation and alkaline depolymerization
Tinzaparin	Heparinase digestion

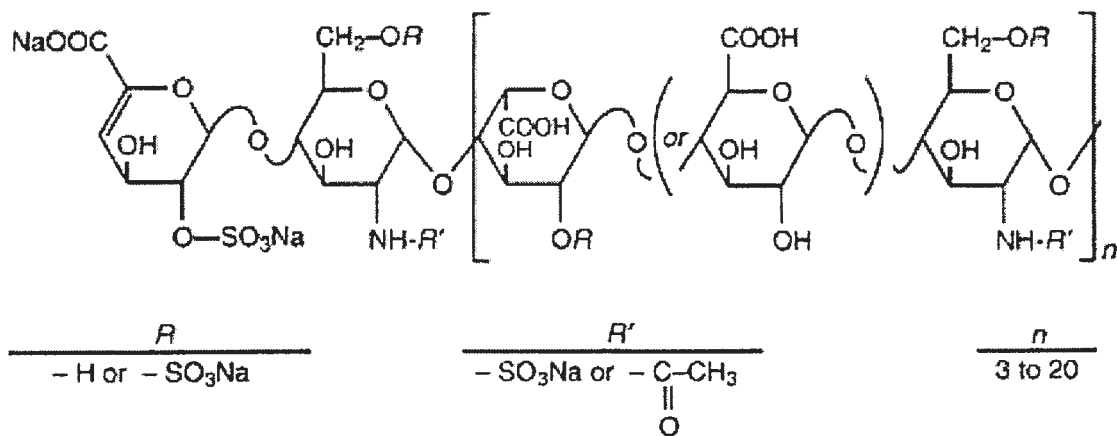
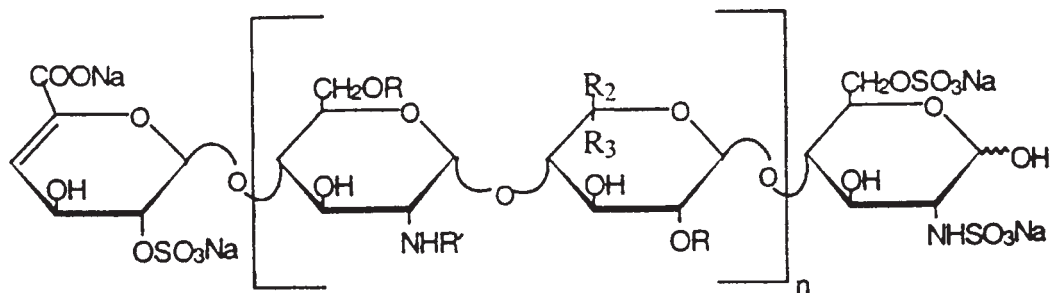
differ. Tinzaparin demonstrated the longest half-life (111–234 min), followed by enoxaparin (129–180 min), then dalteparin (119–139 min).<sup>1, 4-6, 9</sup>

Using prophylactic dosages, the pharmacokinetic properties of dalteparin, enoxaparin, and nadroparin were directly compared.<sup>10</sup> The plasma anti-Xa area under the concentration-time curve (AUC) activities of dalteparin, enoxaparin, and nadroparin were investigated at dosages administered for prevention of DVT. Enoxaparin 40 mg (4000 IU anti-Xa) achieved a statistically significant larger AUC compared with both dalteparin 5000 IU anti-Xa and nadroparin 3075 IU anti-Xa. On the other hand, the AUC of nadroparin was significantly higher compared with dalteparin.

The plasma anti-Xa half-lives after prophylactic dosages of dalteparin 5000 IU anti-Xa, enoxaparin 4000 IU anti-Xa, and tinzaparin 50 IU/kg anti-Xa were compared.<sup>11</sup> Enoxaparin demonstrated the longest anti-Xa half-life compared with both dalteparin and tinzaparin. No statistical difference existed between the half-lives of dalteparin and tinzaparin. Other differences among the LMWHs relate to the inhibitory activities against factor Xa and thrombin. Enoxaparin has the highest anti-Xa:IIa ratio, followed by tinzaparin, then dalteparin.<sup>1, 6</sup>

**Dalteparin**

$R = H$  or  $SO_3Na$   
 $R_1 = COCH_3$  or  $SO_3Na$   
 $R_2 = H$  or  $R_3 = COONa$   
 or  
 $R_2 = COONa$   $R_3 = H$   
 $n = 3-20$

**Enoxaparin****Tinzaparin**

$n = 1$  to  $25$ ,  $R = H$  or  $SO_3Na$ ,  $R' = H$  or  $SO_3Na$  or  $COCH_3$   
 $R_2 = H$  and  $R_3 = COONa$  or  $R_2 = COONa$  and  $R_3 = H$

Figure 1. Molecular structures of dalteparin, enoxaparin, and tinzaparin.<sup>4-6</sup>

**Table 3. Properties of Low-Molecular-Weight Heparin Products<sup>1, 4-6, 9</sup>**

Agent	Mean Molecular Weight (daltons)	Plasma Half-Life (min)	Anti-Xa:Anti-IIa Activity Ratio
Dalteparin	6000	119-139	2.7
Enoxaparin	4200	129-180	3.8
Tinzaparin	4500	111-234	2.8

**Table 4. Biologic Actions of Low-Molecular-Weight Heparins<sup>12</sup>**

Antithrombin-Mediated Actions	Non-antithrombin-Mediated Actions
Anti-Xa activity	Release of tissue-factor-pathway inhibitor
Anti-IIa activity	Suppression of von Willebrand factor release
	Interaction with heparin cofactor II
	Inhibition of leukocyte procoagulant actions
	Promotion of fibrinolysis
	Protein binding
	Modulation of vascular endothelium (receptor and nonreceptor mediated)

### Antithrombin- and Non-antithrombin-Mediated Actions

In addition to antithrombin III-mediated effects (anti-Xa and anti-IIa effects), LMWHs are further differentiated based on recent recognition that non-antithrombin III-mediated actions and other cellular and vascular interactions contribute to the therapeutic effect of LMWHs (Table 4).<sup>12</sup> Non-antithrombin III-mediated actions include the release of tissue factor pathway inhibitor (TFPI), suppression of von Willebrand factor (vWF) release, interaction with heparin cofactor II, inhibition of leukocyte procoagulant actions, promotion of fibrinolysis, and modulation of vascular endothelium.<sup>12</sup>

The LMWHs stimulate the release of TFPI from the endothelium and enhance its inhibitory activity against factor Xa.<sup>13</sup> In one study,<sup>7</sup> the pattern of TFPI release was investigated in six LMWHs (certoparin, dalteparin, enoxaparin, nadroparin, tinzaparin, reviparin) after an intravenous injection of LMWH 100 IU/kg anti-Xa to primates. Each LMWH displayed a different release pattern of TFPI, with tinzaparin having the highest TFPI release after intravenous administration, followed by enoxaparin and dalteparin. In a similar study, the pattern of TFPI release after subcutaneous injection of LMWH 100 IU/kg anti-Xa to primates was evaluated. Of the six LMWHs studied (certoparin, enoxaparin, fraxiparin, nadroparin, tinzaparin, reviparin), enoxaparin produced the highest concentration of free TFPI.<sup>14</sup>

No large human studies clearly demonstrate which LMWH agent releases the most TFPI. Varying patterns of release could lead to different degrees of anticoagulation. Interestingly, preliminary research suggests that TFPI displays an antiangiogenic effect, thus explaining some of the beneficial effect noted in cancer survival. In fact, evidence indicates that LMWHs inhibit angiogenesis, which appears unrelated to the anticoagulant effects of the heparin products.<sup>15</sup> Because this biochemical difference may translate into clinically important variations, the physiologic role of TFPI requires additional clinical investigations.

Recent clinical research found a correlation between LMWHs and vWF release. Von Willebrand factor plays an important role in hemostasis. Secretion of vWF from endothelial cells and platelets promotes platelet aggregation and adhesion to the exposed vascular subendothelium.<sup>16</sup> In addition, vWF is involved in the coagulation cascade by binding to factor VIII, thereby preventing inactivation of factor VIIIa by activated protein C and consequently promoting factor Xa and factor IIa generation through the intrinsic coagulation cascade.<sup>1, 16, 17</sup>

Von Willebrand factor is a marker of platelet stimulation and adverse clinical outcomes. It appears that each LMWH demonstrates a different effect on vWF release. In a recent study, the differing patterns of vWF release among dalteparin, enoxaparin, and UFH were demonstrated in patients after acute coronary events.<sup>18</sup> This difference is important due to a

**Table 5. FDA-Approved Indications for Low-Molecular-Weight Heparins<sup>4-6</sup>**

FDA-Approved Indication	Dalteparin	Enoxaparin	Tinzaparin
Prophylaxis			
Total hip arthroplasty	X	X	
Total knee arthroplasty		X	
General surgery	X	X	
Medically ill		X	
Treatment			
Acute coronary syndrome	X	X	
DVT with or without PE in conjunction with warfarin			X
Inpatient DVT with or without PE		X	
Outpatient DVT		X	

DVT = deep vein thrombosis; PE = pulmonary embolism.

**Table 6. FDA-Approved and Non-FDA-Approved Dosages for Low-Molecular-Weight Heparins<sup>1, 4-6</sup>**

Indications	Enoxaparin	Dalteparin	Tinzaparin
Hip replacement surgery (prophylaxis)	30 mg s.c. q12h started 12–24 hrs after surgery <sup>a</sup> or 40 mg s.c. q24h started 12 hrs before surgery <sup>a</sup> ; extended prophylaxis may be given for up to 3 wks <sup>a</sup>	2500 IU s.c. given 2 hrs before surgery, followed by 2500 IU s.c. the evening after surgery and at least 6 hrs after the first dose, then 5000 IU s.c. q24h <sup>a</sup> ; or 5000 IU s.c. q24h started the evening before surgery <sup>a</sup> ; or 2500 IU s.c. started 4–8 hrs after surgery, then 5000 IU s.c. q24h	50 IU/kg q24h started the evening before surgery or 12 hrs after surgery
Knee replacement surgery (prophylaxis)	30 mg s.c. q12h started 12–24 hrs before surgery <sup>a</sup>	No data	50 IU/kg q24h started the evening before surgery or 12 hrs after surgery
Abdominal surgery (prophylaxis)	40 mg s.c. q24h started 2 hrs before surgery <sup>a</sup>	2500 IU s.c. started 1–2 hrs before surgery, then q24h <sup>a</sup> Patients with malignancy: 5000 IU s.c. the evening before surgery, then 5000 IU s.c. q24h <sup>a</sup> ; or 2500 IU s.c. 1–2 hrs before surgery, then 2500 IU 12 hrs after surgery, followed by 5000 IU s.c. q24h <sup>a</sup>	3500 IU s.c. started 1–2 hrs before surgery
DVT treatment (with or without PE)	1 mg/kg s.c. q12h <sup>a</sup> or 1.5 mg/kg s.c. q24h <sup>b</sup>	100 IU/kg s.c. q12h or 200 IU/kg s.c. q24h	175 IU/kg s.c. q24h <sup>a</sup>
Unstable angina or non-Q-wave MI	1 mg/kg s.c. q12h	120 IU/kg s.c. q12h	No data

MI = myocardial infarction.

<sup>a</sup>FDA-approved dosage for indication.

<sup>b</sup>FDA-approved dosage for inpatient use.

direct correlation between the extent of vWF release and clinical outcomes in patients with acute coronary syndrome. Patients with high vWF release within the first 48 hours after a coronary event had worse clinical outcomes than those whose level was not as high. Those patients who experienced adverse clinical outcomes such as death, myocardial infarction, or

the need for urgent revascularization had a 7-fold higher vWF level than those who did not experience these outcomes.<sup>19</sup>

Compared with UFH, vWF release was statistically lower in patients treated with enoxaparin. On the other hand, patients receiving dalteparin and UFH demonstrated similar release of vWF.<sup>18</sup> This distinct effect of

**Table 7. Clinical Evidence in Venous Thromboembolism Prophylaxis<sup>1, 26</sup>**

Indication	Dalteparin	Enoxaparin	Tinzaparin
Hip replacement (postoperative)	+	+	+
Hip replacement (extended prophylaxis)	+	+	-
Knee replacement	-	+	+
Orthopedic trauma	-	+	-
General surgery	+	+	+
Spinal cord injury	-	+	+
Medically ill	-	+	-
Neurosurgery	-	+	-

**Table 8. Clinical Evidence in Venous Thromboembolism Treatment<sup>1, 27</sup>**

Indication	Dalteparin	Enoxaparin	Tinzaparin
Deep vein thrombosis	+	+	+
Pulmonary embolism	+	+	+

vWF might explain the dichotomy observed with the LMWH trials in acute coronary syndrome. Dalteparin failed to demonstrate superiority to UFH in the Fragmin in Unstable Coronary Artery Disease (FRIC) trial.<sup>20</sup> In contrast, enoxaparin was proven twice to be superior to UFH in both the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave Myocardial Infarction (ESSENCE) and Thrombolysis in Myocardial Infarction (TIMI)-11B trials in the 30-day composite end points of death, myocardial infarction, recurrent angina, or urgent revascularization.<sup>21-23</sup> Tinzaparin was not tested in this patient population. Short of having a head-to-head trial testing their relative benefits, these findings suggest that important differences in efficacy exist among LMWHs in treating coronary artery disease.

It has been mentioned that the methodology used in the ESSENCE, FRIC, and TIMI 11B trials varied, which could account for their relative differences in efficacy. It should be noted, however, that the widely publicized theory of difference in quality of dosing of UFH arms to explain the outcomes from those trials was recently refuted. It was first believed that the dosing of UFH in the comparative arm of the enoxaparin trial was suboptimal since it did not reach therapeutic activated partial thromboplastin time (aPTT) in all patients at 24 hours. Critics theorized that if the patients in the UFH arm achieved all therapeutic aPTTs within the first 24 hours, enoxaparin would have not demonstrated superiority over UFH. This theory was revoked

in a recent published study. In fact, enoxaparin was shown to improve outcomes compared with UFH at any levels of aPTT achieved.<sup>24</sup>

### Thrombus Formation

In a model of thrombus induced by the ligation of the inferior vena cava in mice, the antithrombotic and antiinflammatory properties of LMWHs during stasis-induced venous thrombosis were compared.<sup>25</sup> It was found that enoxaparin prevented more thrombus formation compared with dalteparin or placebo. In addition, less vein-wall neutrophils and total inflammatory cells were present in the enoxaparin group compared with dalteparin and placebo. Tinzaparin was not tested in this animal model.<sup>25</sup>

### FDA Status and Clinical Evidence

The FDA-approved indications for dalteparin, enoxaparin, and tinzaparin in the U.S. market differ (Table 5).<sup>4-6</sup> In addition, all three LMWHs have clinical evidence reported in the literature for various treatment indications for which they do not have FDA approval (Tables 6-9).<sup>1, 4-6, 26-28</sup> Dalteparin has literature to support its use for the treatment of DVT and PE. Enoxaparin has safety and efficacy data to support its use in multiple trauma and neurosurgery. There is evidence to support tinzaparin for DVT prophylaxis in general surgery, total hip arthroplasty, and total knee arthroplasty.

Although published evidence can be found for different clinical applications for each LMWH,

**Table 9. Clinical Evidence in Acute Coronary Syndrome Treatment<sup>1, 28</sup>**

Indication	Dalteparin	Enoxaparin	Tinzaparin
Unstable angina or non-ST elevation myocardial infarction			
Acute treatment, no intervention	+	+	-
Acute treatment with intervention	+	+	-

one should be careful not to extrapolate the data from one molecule to the other. Clinicians and formulary decision-makers should evaluate all the available literature carefully before recommending an agent and a specific dosing regimen for a specific condition. Clinicians should refrain from using a LMWH for any indication until the efficacy or safety of the agent is objectively tested.

As an example, in a double-blind, randomized clinical trial, 90 patients with hip fractures were given dalteparin prophylactically for DVT. Patients were randomized to receive dalteparin 2500 U before surgery, followed by UFH 5000 U every 8 hours or dalteparin 5000 U after surgery for 9 days. Both groups had similar type and extent of fracture and surgery. A statistically significant increase in the rate of PE on lung scan and in the rate of DVT on venography was found in the dalteparin group, suggesting that subcutaneous UFH was superior to subcutaneous dalteparin for DVT prophylaxis in this patient population.<sup>29</sup> Those findings should discourage a clinician from using dalteparin in patients with hip fractures.

When interpreting data about LMWHs, variations in the design and methods of the clinical trials must be considered. In addition, significant variations are noted in patient selection, dosages of the agents, active treatment duration, and the definition and assessment of end points. As a result, meta-analyses should be interpreted with caution. Several meta-analyses have been performed that pooled the results of controlled clinical trials comparing LMWHs and intravenous UFH for the treatment of DVT.<sup>30-35</sup> Clinical benefits were clearly achieved with LMWH over UFH. However, it was not clear which LMWH agent was superior.

A recent meta-analysis compared five LMWH products with UFH.<sup>31</sup> The investigators stated, "based on the pooled results there are no major differences among preparations. This suggests that the use of any of the products in the dosages evaluated in the trials is reasonable."<sup>31</sup> The authors added, "however, this conclusion is

limited and must be tempered by the fact that the comparison of LMWH products is indirect...it is impossible to make definitive conclusions about their relative safety and efficacy."<sup>31</sup> This analysis therefore could not prove or refute any clinical differences among the LMWHs. Because the LMWHs are not interchangeable and are different entities, the strength of a meta-analytic approach must be questioned, and only prospective, well-designed, comparative trials could help answer if the agents are clinically interchangeable.

#### Dosing Intervals and Practical Issues

The LMWHs require different dosing intervals when treating DVT or PE. Tinzaparin is safe and effective as a once-daily agent for the treatment of DVT and PE.<sup>36, 37</sup> Enoxaparin also has been shown to be safe and effective as a once- or twice-daily agent. There is cause for concern about a trend toward more recurrent thromboembolism when using once-daily enoxaparin compared with twice-daily. The patient population of concern includes those who are receiving treatment for DVT with or without PE who have cancer or are obese. Although the absolute recurrence rate of venous thromboembolism was nearly doubled in this patient population, these differences did not reach statistical significance.<sup>38</sup>

On the other hand, dalteparin is clearly best used in a twice-daily regimen when used for the treatment of DVT or PE. In a randomized study, dalteparin was evaluated in 140 patients with iliofemoral DVT. Patients were administered dalteparin 200 IU/kg once/day versus 100 IU/kg twice/day. The once-daily treatment arm had a statistically significant higher rate of symptomatic PE at 10 days; the twice-daily regimen therefore is recommended for dalteparin.<sup>39</sup>

Practical issues should be considered when selecting a LMWH. Prefilled syringes are available for treatment doses of enoxaparin, and multidose vials are available for treatment doses of dalteparin and tinzaparin. Small amounts of benzyl alcohol are present in the multidose vials.<sup>4-6</sup>

## Distinct Entities

Based on the chemical and pharmacologic distinct attributes and the expanding clinical roles of LMWHs, several organizations including the FDA,<sup>40</sup> the American College of Chest Physicians,<sup>27</sup> the International Cardiology Forum,<sup>41</sup> the American College of Cardiology, and the American Heart Association<sup>42</sup> published statements supporting LMWHs to be distinct pharmacologic entities. The FDA stated, "LMWH can not be used interchangeably, unit for unit, with heparin, nor can one individual LMWH be used interchangeably with another."<sup>40</sup> The American College of Chest Physicians stated, "properties associated with one LMWH cannot be extrapolated to a different LMWH. Findings of clinical trials apply only to the particular LMWH evaluated and should not be generalized to the LMWH at large. Some of these LMWHs are prepared by different methods of depolymerization and differ to some extent in their pharmacokinetic properties and anticoagulant profile, they may not be clinically interchangeable."<sup>27</sup> The American College of Cardiology and the American Heart Association noted that "although LMWHs share many pharmacological similarities, they also vary in important aspects, and it is important to consider each drug individually rather than as members of a class of interchangeable compounds."<sup>42</sup>

It is a consensus from these groups that properties associated with one LMWH cannot be extrapolated to a different LMWH. Treatment decisions should be based on the available safety and efficacy data for each LMWH.

## Conclusion

The LMWHs are distinct compounds that possess unique chemical, pharmacokinetic, and pharmacodynamic profiles. Each agent has dissimilar antithrombotic activities, which are reflected by antithrombin- (anti-Xa and anti-IIa ratio) and non-antithrombin-mediated actions. The LMWHs have shown divergent results in clinical trials; it is not possible to draw conclusions with regard to their relative clinical efficacies. As a result, several national organizations support the concept that the LMWHs are distinct entities and are not therapeutically interchangeable. In the absence of comparative studies, clinical results of one molecule should not be extrapolated to another. An evidence-based approach is necessary for selecting a LMWH. Treatment decisions should

be based on the available safety and efficacy data for each LMWH. Agents should be prescribed only for those indications for which they have been shown to be effective and only at dosages that have been studied. Each LMWH should be considered unique until scientifically sound comparative trials are performed.

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