INNOVANCE Heparin

Increasing Safety and Efficiency in Heparin Therapy Management
The INNOVANCE Heparin Assay—Increasing Safety and Efficiency in Heparin Therapy Management

Heparin and Its Clinical Applications

Heparin is a highly sulfated mucopolysaccharide typically prepared from porcine or bovine gut mucosa and used clinically as an anticoagulant for intravenous or subcutaneous application. Heparins are heterogeneous with respect to molecular size, anticoagulant activity, and pharmacokinetic properties.

Heparin is available for clinical use in two common forms: natural, unfractionated heparin (UFH), with a mean molecular size of about 15,000 kDa, and low-molecular-weight heparin (LMWH), with a typical mean molecular size of 5,000 kDa. LMWH can be derived from UFH by chemical or enzymatic depolymerization.

Both UFH and LMWH require antithrombin as a cofactor for their anticoagulant activity. Both heparin types accelerate FXa (and FIXa, FXIa, and FXIIa) inactivation, while UFH also inactivates thrombin (anti-IIa activity). The minimum length of the polysaccharide chain required for anti-Xa activity is 5 units, whereas anti-IIa activity requires polysaccharide chains of at least 18 units. Such longer polysaccharide chains are present in significant amounts only in UFH.

Despite being more expensive, LMWH has replaced UFH in many clinical applications because it offers certain advantages:

• Less heparin-induced thrombocytopenia (HIT), a severe complication of heparin therapy with a high mortality rate
• Therapeutic use by subcutaneous rather than intravenous application
• No routine monitoring required
• Less bone destruction with long-term use

Nevertheless, in certain indications, UFH is the preferred heparin, e.g., for hemodialysis or extra-corporal circulation, or patients with severe kidney disease.

Mechanism of action of unfractionated and low-molecular-weight heparin

To inactivate thrombin, UFH forms a ternary complex with antithrombin and thrombin. Because of their lower molecular weight, LMWH species are unable to form the ternary complexes with antithrombin and thrombin. Thus, LMWHs produce their anticoagulant effect mainly by inhibiting factor Xa.
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### Characteristics of LMWH and UFH

<table>
<thead>
<tr>
<th></th>
<th>LMWH</th>
<th>UFH</th>
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<tbody>
<tr>
<td><strong>Molecular size</strong></td>
<td>Mean: 5,000 kDa;</td>
<td>Mean: 15,000 kDa;</td>
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<tr>
<td></td>
<td>Range: 2,000–9,000 kDa</td>
<td>Range: 3,000–90,000 kDa</td>
</tr>
<tr>
<td><strong>Molecular targets</strong></td>
<td>Reduced anti-IIa activity relative to anti-Xa activity</td>
<td>Anti-IIa and anti-Xa activity</td>
</tr>
<tr>
<td><strong>Plasma half-life</strong></td>
<td>About 3–6 hours</td>
<td>Highly variable and dose-dependent 30–150 min</td>
</tr>
<tr>
<td><strong>Route of application</strong></td>
<td>Subcutaneous (once or twice daily)</td>
<td>Intravenous (continuous infusion) or subcutaneous (twice daily)</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>More predictable anticoagulant response; no routine monitoring required</td>
<td>Requires monitoring in therapeutic concentration Anti-Xa assay only APTT or anti-Xa assay</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>Renal clearance</td>
<td>Larger molecules are cleared more rapidly than smaller; only partial renal clearance</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Reduced complex formation, resulting in less HIT antibodies</td>
<td>Complex formation with PF4 (platelet factor 4), which may induce HIT antibodies</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Lower risk of osteoporosis</td>
<td>Long-term use associated with bone loss</td>
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**Molecular weight distribution of LMWH and UFH**

![Molecular weight distribution graph](image)

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Heparin therapy modalities

**UFH** is the preferred drug in patients with severe kidney disease, and for situations where very high anticoagulant levels are required. Neutralization of UFH is possible by complexation with protamine. Applications for UFH include:

- **Prophylactic regimen for prevention of venous thromboembolism (VTE),** although UFH has been nearly completely replaced by LMWH for this purpose. Typically administered twice daily subcutaneously. No monitoring is required.
- **Therapeutic regimen for therapy of VTE or special situations with high coagulation triggering activity,** such as hemodialysis or extra-corporal circulation. Administered by continuous intravenous infusion. Routine monitoring by APTT or anti-Xa assay is required.

**LMWH** is the drug of choice for most heparin-therapy applications. There is a risk of accumulation in kidney-disease patients, and no real antidote is available; protamine is only partially effective. Applications for LMWH include:

- **Prophylactic regimen for prevention of VTE.** LMWH has become the standard routine prophylaxis for VTE. Typically administered once daily subcutaneously. No monitoring is required.
- **Therapeutic dosing for therapy of VTE.** Dosing must be adjusted for body weight. Administered once or twice daily subcutaneously. Routine monitoring is not required, but for specific indications, such as obese patients, infants, pregnancy, or patients with renal impairment; monitoring is recommended and can be performed via anti-Xa assay only.

A very small and special heparinoid is **fondaparinux.** This synthetic pentasaccharide analog is the smallest polysaccharide with anticoagulant activity. Fondaparinux acts only through anti-Xa activity potentiation, has an increased half-life versus LMWH, and is exclusively cleared by the kidneys. Monitoring is not recommended on a routine basis, but, if indicated, a fondaparinux-specific anti-Xa assay is the method of choice. When monitoring is indicated, fondaparinux is required for assay calibration.

Target population for anti-Xa testing

1. All patients under LWMH therapy who should be monitored, such as:
   - Pregnant women
   - Infants and children
   - Patients with renal impairment
   - Patients with high risk for bleeding or recurrences
   - Very obese and very underweight patients
2. Patients under UFH therapy who show an abnormal baseline APTT, including:
   - Patients with liver cirrhosis
   - Patients in the bridging phase from coumadin therapy
   - Patients with lupus anticoagulants
   - Patients under or having completed thrombolytic therapy
   - Patients with congenital or acquired factor deficiencies
   - Critically ill patients
   - Patients with APTT prolongation due to high C reactive protein (CRP) levels

Recommended therapeutic target ranges\(^1\)\(^-\)\(^3\)

APTT therapeutic ranges must be calibrated versus anti-Xa activity as specified below:

<table>
<thead>
<tr>
<th>Target Range for Anti-Xa Activity</th>
<th>Timing for Testing</th>
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<tr>
<td>LMWH 0.6–1.0 IU/mL</td>
<td>At peak level 4 hours after application</td>
</tr>
<tr>
<td>UFH 0.3–0.7 IU/mL</td>
<td>4–6 hours after initiation or dose adjustment</td>
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For more-specific information, please refer to the prescribing information provided by the heparin manufacturers.
The Anti-Xa Assay: A Better Choice for UFH Monitoring

The APTT test is affected by many biological factors unrelated to heparin concentration and is not a standardized test. The historical goal of 1.5–2.5 times prolongation of the APTT is considered an antiquated and unsafe practice.

The full effect of the preanalytical, analytical, and biological variables became apparent when it was demonstrated that less than half of the variation in APTT values in patients receiving heparin was explained by differences in heparin concentrations.

Clinical data from the last 10–20 years support a conversion from APTT to anti-Xa monitoring. Advantages of anti-Xa monitoring include:

- A smoother dose-response curve
- More-stable heparin levels during therapy
- Fewer blood samples required
- Fewer dosage adjustments

Increasing data suggest that fewer overall laboratory tests are necessary when the anti-Xa assay is used, due to its smoother dose-response curve. Consequently, although the cost per anti-Xa assay is higher than that of the APTT test, overall institutional costs may be nearly equivalent due to the fewer monitoring tests and dosage adjustments necessary when the anti-Xa assay is used.

Several recent studies support the use of anti-Xa assays for UFH monitoring:

- Vandiver reports for the use of an anti-Xa assay-based UFH-monitoring protocol a higher percentage of within-range blood plasma heparin monitoring tests, fewer monitoring tests for the patient to achieve blood plasma monitoring tests within goal range, and fewer dose adjustments compared with a protocol based on blood plasma monitoring using the APTT.
- Liveris found the anti-Xa assay to correlate better with heparin dosing than ACT or APTT. In pediatric extracorporeal membrane oxygenation, the anti-Xa assay was a more valuable monitor of heparin administration.
- Adatya observed a high rate (74%) of discordant results between APTT and anti-Xa in patients with left ventricular assist devices. Many of the discordant results were related either to bridging from warfarin therapy or presence of hemolysis, which may falsely elevate APTT.
- Van Roessel investigated critically ill patients; paired analysis of APTT and anti-Xa was discordant in 63% of the samples. Anti-Xa heparin levels were considered the gold standard; APTT was neither sensitive nor specific to detect under- or overdosing.

Distribution of APTT and anti-Xa levels in critically ill patients
INNOVANCE Heparin Assay: Hybrid Calibration Improves Reliability and Efficiency

An important new feature of the INNOVANCE® Heparin assay from Siemens Healthcare Diagnostics is that only one reference curve and a universal calibrator set are required for measurement of both UFH and LMWH samples. The universal calibrator set is traceable to the international reference preparations for both UFH and LMWH.

Current guidelines and recommendations point to the need for different calibrators for UFH and LMWH. However, with the INNOVANCE Heparin assay, equal units of UFH and LMWH correspond to the same measuring signal, i.e., the same absorbance signal is obtained, irrespective of whether 0.5 IU/mL of UFH or LMWH is present in the sample. This is made possible by the specific, sophisticated assay conditions of the INNOVANCE Heparin assay, allowing the use of a single calibration curve for samples containing either UFH or LMWH.

Note: The guidelines do not include assays that utilize hybrid calibration because no commercial assays with this feature were available at the time the guidelines were established.

Hybrid calibration saves time, eliminates potential errors, and improves patient safety

In many cases, the lab does not receive information specifying which type of heparin a specific patient is receiving. Incorrectly allocating the sample to either a UFH-calibrated or LMWH-calibrated heparin assay results in an erroneous heparin concentration, with all the consequences that may arise from such an invalid result. To prevent this from happening, labs often spend considerable time and effort to get this important information.

Now, with the INNOVANCE Heparin assay, heparin samples can be tested immediately, without having to verify which type of heparin the patient is receiving. Benefits to the lab include the ability to run fewer heparin assays overall and lower costs for calibration materials, as well as substantial time savings for lab personnel and the ability to deliver heparin test results more quickly. But the most important benefit is the improved patient safety that results from eliminating interpretation errors and getting the correct result regardless of which type of heparin is used.

INNOVANCE Heparin Assay: 2nd International Standard for LMWH compared to the 6th International Standard for UFH

![Graph showing comparison between UFH-6th International Standard and LMWH-2nd International Standard.](chart.png)
References


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