Anticoagulation in special patient populations: Are special dosing considerations required?

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ABSTRACT
Optimal dosing of low-molecular-weight heparin (LMWH) therapy has not yet been established for patients with morbid obesity or renal insufficiency or for pregnant women. Monitoring of anti-Xa levels appears to be helpful in guiding LMWH dosing in all of these patient groups. Use of fondaparinux in these populations has yet to be defined. Cancer patients are at particular risk of venous thromboembolism and generally require escalated and/or prolonged anticoagulation with intense monitoring of therapy.

The introduction of low-molecular-weight heparin (LMWH) was a turning point in the management of thrombotic disorders. Until 1987, the only parenteral anticoagulant was unfractionated heparin (UFH), which is limited by unpredictable pharmacokinetic and pharmacodynamic properties, as detailed earlier in this supplement. LMWH has more consistent and predictable anticoagulant activity, can be given subcutaneously once daily without laboratory monitoring, and has replaced UFH for most indications.

However, LMWH and other newer anticoagulants have not been well studied in several important patient populations, leaving questions as to efficacy, safety, and appropriate dosing. These special populations include morbidly obese patients (weight > 150 kg or body mass index > 50 kg/m²), patients with severe renal insufficiency (creatinine clearance < 30 mL/min), and pregnant women. This article reviews special considerations for anticoagulant therapy—with LMWH and other options—in these populations as well as in cancer patients, who also appear to require escalated or prolonged anticoagulant therapy in the setting of venous thromboembolism (VTE).

MORBIDLY OBESE PATIENTS
Obesity is an increasing health risk for Americans, occurring in approximately one third of both men and women. Obesity is an important risk factor for thrombosis, and VTE is common in obese patients.

LMWH has theoretic advantages in obese patients as a result of superior subcutaneous bioavailability. However, even LMWH at standard fixed doses may not be sufficient to prevent VTE in morbidly obese patients. Frederiksen et al demonstrated a strong negative correlation between total body weight and heparin activity (as measured by anti-Xa assay) with fixed doses of the LMWH enoxaparin. This relationship has also been observed in obese patients who are critically ill. These data suggest that weight-adjusted doses may be more appropriate than fixed doses for VTE prophylaxis in morbidly obese patients.

Scholten et al conducted a nonrandomized retrospective study in 481 obese patients undergoing gastric bypass surgery. In addition to multimodal therapy with mechanical compression stockings, enoxaparin 40 mg every 12 hours was superior to enoxaparin 30 mg every 12 hours with respect to the incidence of postoperative deep vein thrombosis (DVT) (0.6% vs 5.4%; \( P = .01 \)) without an increase in bleeding complications. Yet a smaller randomized study of the LMWH nadroparin (5,700 IU vs 9,500 IU) in 60 bariatric surgery patients failed to show a benefit from the higher dose in preventing postoperative DVT.

It should be noted that heparin activity correlates with LMWH dose even in nonobese patients. Using data from the MEDENOX trial, the efficacious prophylactic dose for enoxaparin (40 mg daily) translates to a dose of 0.5 mg/kg in a typical 80-kg patient. Similarly, an open-label trial evaluating two doses (75 and 175 IU/kg) of the LMWH tinzaparin given to otherwise healthy obese volunteers (100 to 165 kg) concluded that prophylactic tinzaparin dosing should be based on...
SPECIAL PATIENT POPULATIONS

TABLE 1
 Therapeutic peak anti-Xa levels* with low-molecular-weight heparins for treatment of venous thromboembolism

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Absolute dose</th>
<th>Anti-Xa activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin 1 mg/kg every 12 hours</td>
<td>0.6–1.0 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin 1.5 mg/kg daily</td>
<td>1.0–1.5 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Tinzaparin 175 IU/kg daily</td>
<td>0.85–1.0 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Dalteparin 100 IU/kg every 12 hours</td>
<td>0.4–1.1 IU/mL</td>
<td></td>
</tr>
<tr>
<td>Dalteparin 200 IU/kg daily</td>
<td>1.0–2.0 IU/mL</td>
<td></td>
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</tbody>
</table>

* Via chromogenic anti-Xa assay drawn 4 hours after subcutaneous dose

actual body weight, independent of the presence of obesity, and that it need not be capped at a maximal absolute dose.6 These studies support the notion that prophylactic LMWH doses (like therapeutic doses) should be weight-adjusted in all patients, with or without obesity. Although expert consensus generally recommends a heparin concentration of 0.1 to 0.6 IU/mL (by chromogenic anti-Xa assay) to prevent VTE, the optimal heparin activity needed for VTE prophylaxis remains unproven and can vary by LMWH.

Shepherd et al7 recently found that subcutaneous adjusted-dose UFH, targeted to a partial thromboplastin time (PTT) 1.5 times control, is effective in reducing the risk of VTE in bariatric surgery patients. Unfortunately, the difficulties of titrating subcutaneous UFH to a target PTT are well documented,6 raising questions about the overall feasibility of this approach.

To our knowledge, no published studies have looked at dosing of newer anticoagulants, such as the synthetic pentasaccharide fondaparinux, an indirect factor Xa inhibitor, in obese patients.

Recommendations

Without additional data, firm recommendations are difficult; however, clinicians should consider escalating standard recommended doses of LMWH in morbidly obese patients (ie, 0.5 mg/kg for enoxaparin) for thromboprophylaxis with or without adjunctive use of mechanical compression devices or anti-Xa monitoring. Alternatively, subcutaneous adjusted-dose UFH titrated to a PTT value 1.5 times control may be used.

Contemporary VTE treatment trials of LMWH generally used weight-adjusted doses without any ceiling for obese patients. However, few patients with a total body weight greater than 150 kg and a body mass index greater than 50 kg/m² were actually included. The relationship of intravascular volume and total body weight is not linear, and there is concern that dosing based on actual body weight could lead to excessive plasma concentrations of LMWH. However, post hoc analysis of cardiovascular patients using full weight-adjusted doses of LMWH and UFH found no differences in hemorrhage rates between obese and normal weight groups.6 Similarly, anti-Xa activity is not significantly increased when LMWH is administered to obese patients based on total body weight.6,10,11

Given the lack of clinical trial data for VTE treatment with LMWH in obese patients, it is still reasonable to monitor anti-Xa levels in such patients. Therapeutic anti-Xa levels depend on the specific LMWH preparation and dosing interval (Table 1). Dose reduction should be considered if the anti-Xa level is excessive 4 hours after the subcutaneous LMWH dose.

■ PATIENTS WITH RENAL IMPAIRMENT

Because LMWH is cleared by the kidneys, patients with impaired renal function have prolonged elimination of LMWH agents. Thus, patients with severe renal insufficiency may be at increased risk for bleeding with standard doses of LMWH, particularly after multiple doses.

Post hoc analysis of cardiovascular trials using full weight-adjusted doses of LMWH and weight-adjusted and activated PTT (aPTT)-monitored UFH found significant increases in bleeding rates in renally impaired patients in both treatment groups.9 A recent retrospective analysis using full weight-adjusted doses of LMWH or weight-adjusted and aPTT-monitored UFH confirmed this finding.12 The study involved 620 patients with creatinine clearance (CrCl) rates of less than 60 mL/min, of which 331 received UFH, 250 received enoxaparin, and 39 received both. Rates of major bleeding were 26.3 per 1,000 patient-days for UFH and 20.7 per 1,000 patient-days for enoxaparin. Major bleeding complications were similarly increased with both UFH and enoxaparin across categories of worsening renal insufficiency. Among the subgroup of patients with severe renal insufficiency, the rate of minor bleeding was significantly higher in those treated with enoxaparin than in those treated with UFH (incidence ratio, 2.5; 95% confidence interval [CI], 1.01 to 6.36). These data suggest that patients with renal impairment are at increased risk for bleeding and that no specific heparin strategy is inherently safer than the other.

Although UFH has a dual clearance mechanism and may be less prone to accumulation than LMWH in patients with renal insufficiency, UFH has greater adverse effects on platelet function and capillary permeability with respect to bleeding. There is no evidence that UFH should be the “default” anticoagulant in renally impaired patients, provided that appropriate dosing and monitoring of LMWH is followed.
Large contemporary randomized trials of LMWH have generally excluded patients with significant renal impairment. However, sufficient pharmacokinetic and clinical data are available to make dosing recommendations. Pharmacokinetic studies confirm that the anti-Xa activity of LMWH is negatively correlated with CrCl. For enoxaparin the relationship between anti-Xa activity and CrCl is linear in both single-dose and multiple-dose studies, with significantly increased anti-Xa levels in patients with a CrCl less than 30 mL/min. Sanderink et al reported a 39% decrease in anti-Xa clearance and a 35% increase in anti-Xa exposure with multiple prophylactic doses of enoxaparin in patients with a CrCl less than 30 mL/min relative to those with a CrCl of 31 mL/min or greater.

**Recommendations**

The aforementioned studies led to revised US Food and Drug Administration dosing guidelines for enoxaparin in the setting of renal insufficiency (Table 2). It is important to note that the pharmacokinetic effect of impaired renal function may differ among LMWHs, and no such dosing guidelines exist for other LMWHs or for UFH. Moreover, the pentasaccharide fondaparinux is currently contraindicated in patients with renal impairment, owing to its much longer half-life than LMWH and a lack of safety and pharmacokinetic data in this patient group.

It should be emphasized that the dosing recommendations derived from pharmacokinetic studies have not been validated in randomized trials. The cutoff of 30 mL/min for renal dose adjustment cannot be viewed dogmatically, as patients with a CrCl less than 10 mL/min may react differently from those with less renal impairment. Caution should be exercised in anticoagulation in all patients with renal impairment, and monitoring of heparin or anti-Xa activity remains the safest approach.

### PREGNANT WOMEN

The incidence of DVT in pregnant women is about six times the incidence in nonpregnant women. Approximately one of every 100,000 pregnant women dies because of pulmonary embolism (PE), and in developed countries PE is the leading cause of death in pregnant women. Often these events are sudden, occurring without premonitory signs or symptoms in what appeared to be an uneventful pregnancy. Several factors promote thrombosis during pregnancy, including reduced venous outflow from an expanding uterus (promoting stasis) and increased levels of almost all of the clotting proteins in the clotting cascade.

Over the past few years, LMWH has become the choice for VTE treatment and prevention in pregnant women, owing to its improved bioavailability, better safety profile with regard to osteoporosis and thrombocytopenia, and significantly reduced monitoring requirements relative to UFH. However, during pregnancy the volume of distribution and clearance of LMWH must be considered. The volume of distribution of LMWH is higher throughout pregnancy, and clearance may be higher in early pregnancy and then decline as pregnancy progresses to delivery. In light of this, anti-Xa levels should be assessed during the first week of pregnancy and then at least once per month in each trimester. The desired anti-Xa range for prophylaxis is 0.1 to 0.3 IU/mL, and the treatment range is 0.4 to 2.0 IU/mL (Table 1). In the postpartum period the volume of distribution and clearance will decrease further, requiring continued monitoring.

### Intensity and duration of prophylaxis

The intensity and length of VTE prophylaxis in pregnancy depends on the patient’s history of VTE. We recommend that pregnant women with a single previous VTE event secondary to a transient risk factor have clinical surveillance for signs and symptoms of VTE and receive 4 to 6 weeks of postpartum prophylaxis with LMWH (enoxaparin 40 mg or dalteparin 5,000 IU daily) as single-agent therapy or cross over to warfarin (dosed to achieve an international normalized ratio [INR] of 2.0 to 3.0). When the initial VTE event was secondary to prior pregnancy, estrogens, or additional risk factors (eg, obesity) or was a single idiopathic VTE event (and the patient is no longer on long-term anticoagulation), then antepartum prophylaxis is recommended with LMWH (enoxaparin 40 mg or dalteparin 5,000 IU daily) followed by postpartum prophylaxis as noted above. If the VTE event was secondary to thrombophilia or there is a strong family history of thrombophilia and a personal history of VTE, we...
We recommend that pregnant women with antiphospholipid antibody syndrome who are receiving warfarin can be used safely in breast-feeding women.

Pregnant women with additional considerations

We recommend that pregnant women with antiphospholipid antibodies and a history of two or more early or late pregnancy losses, preeclampsia, intrauterine growth retardation, or abortion receive antepartum aspirin plus LMWH (enoxaparin 40 mg or dalteparin 5,000 IU daily) and 4 to 6 weeks of postpartum prophylaxis. This is the same regimen recommended for women with known thrombophilia, recurrent miscarriages, a second-trimester or later loss, severe or recurrent preeclampsia, or abortion. Patients with antiphospholipid antibody syndrome who are receiving long-term warfarin therapy should be converted to adjusted-dose LMWH, which should be maintained up to the time of delivery and restarted after delivery until a therapeutic INR is achieved.

Pregnant women with mechanical heart valves should receive either adjusted-dose UFH targeted to a therapeutic aPTT (heparin level of 0.35 to 0.70 IU/mL) or adjusted-dose LMWH with a desired 4-hour postdose anti-Xa level of 1 to 2.2 IU/mL.\(^2\) As the pregnancy progresses, bimonthly monitoring of anti-Xa levels with empiric dose adjustments is indicated, in light of the changes in the volume of distribution and clearance of LMWH as pregnancy progresses.

Pregnant women on prophylactic doses of LMWH have few bleeding complications with spontaneous delivery. Prophylactic doses can be held once labor begins. For patients on full weight-adjusted LMWH doses, the LMWH should be discontinued 24 hours before elective induction of labor; if the woman is deemed to have a very high risk of recurrent VTE, therapeutic UFH can be initiated intravenously and discontinued 4 to 6 hours before the expected time of delivery.

### TABLE 3
Dosing regimens for LMWHs in pregnancy

<table>
<thead>
<tr>
<th>Prophylactic LMWH</th>
<th>Intermediate-dose prophylactic LMWH</th>
<th>Adjusted-dose LMWH titrated via anti-Xa monitoring</th>
<th>Postpartum prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Dalteparin 5,000 IU or enoxaparin 40 mg daily</em></td>
<td><em>Dalteparin 5,000 IU or enoxaparin 40 mg twice daily</em></td>
<td><em>Dalteparin 100 IU/kg or enoxaparin 1 mg/kg twice daily</em></td>
<td><em>Warfarin for 4 to 6 weeks to a target INR of 2.0 to 3.0</em></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Dalteparin 5,000 IU or enoxaparin 40 mg daily</th>
</tr>
</thead>
</table>
| Continued 4 to 6 hours before the expected time of delivery. Prophylactic doses can be held once labor begins. For patients on full weight-adjusted LMWH doses, the LMWH should be discontinued 24 hours before elective induction of labor; if the woman is deemed to have a very high risk of recurrent VTE, therapeutic UFH can be initiated intravenously and discontinued 4 to 6 hours before the expected time of delivery.

### TABLE 4
VTE prophylaxis and treatment in cancer patients

<table>
<thead>
<tr>
<th>VTE prophylaxis for the surgical patient</th>
<th>VTE prophylaxis for the medical patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-risk patient</strong></td>
<td><strong>Very-high-risk patient</strong></td>
</tr>
<tr>
<td><em>Dalteparin 5,000 IU daily</em></td>
<td><em>UFH 5,000 U every 8 hr</em></td>
</tr>
<tr>
<td><em>Dalteparin 5,000 IU daily</em></td>
<td><em>Enoxaparin 40 mg daily</em></td>
</tr>
<tr>
<td><em>Dalteparin 5,000 IU daily</em></td>
<td><em>UFH 5,000 U 2 hr preoperatively, then every 8 hr</em></td>
</tr>
<tr>
<td><em>Dalteparin 5,000 IU daily</em></td>
<td><em>Enoxaparin 40 mg or dalteparin 5,000 IU daily</em></td>
</tr>
</tbody>
</table>

### VTE treatment

| UFH 80 U/kg bolus, 18 U/kg/hr infusion (aPTT every 6 hr for duration of infusion, adjust dose to a target heparin level) with concomitant warfarin* | UFH 5,000 U 2 hr preoperatively, then every 8 hr |
| UFH (enoxaparin 1 mg/kg every 12 hr, or tinzaparin 175 IU/kg daily) with concomitant warfarin* | Enoxaparin 40 mg or dalteparin 5,000 IU daily |
| UFH (enoxaparin 1 mg/kg daily) with concomitant warfarin* | UFH, Enoxaparin, or Dalteparin |

### PATIENTS WITH CANCER

An association between venous thrombosis and malignant disease was first documented in the 1860s. Clinically manifested VTE has been reported in approximately 15% of cancer patients; rates including subclinical disease are probably even higher.\(^2\) Some types of cancer have a higher prothrombotic tendency, but this feature is affected by disease staging, chemotherapy, surgical intervention, and generalized debility. Cancer patients with VTE who are receiving anticoagulation have twice the rate of recurrence on treatment as do noncancer patients; they also are hospitalized longer, pose more difficulties for maintenance...
Prophylaxis in cancer patients undergoing surgery

Because of cancer’s association with increased thrombogenicity, cancer patients undergoing surgery should be considered at high or very high risk for VTE (Table 4). Cancer patients at high risk are generally those under 60 years of age without additional VTE risk factors. In the absence of prophylaxis, the incidences of proximal DVT and fatal PE in these patients are about 4% to 8% and 0.4% to 1%, respectively. Most cancer patients undergoing surgery will be in the very-high-risk group, i.e., over 60 years of age with multiple risk factors. In these patients, the incidences of proximal DVT and fatal PE are about 10% to 20% and 0.2% to 1%, respectively. In these patients, the incidences of proximal DVT and fatal PE are about 10% to 20% and 0.2% to 1%, respectively.

Treatment of acute VTE in cancer patients

Treatment of acute VTE in patients with malignancy should include weight-based UFH or weight-adjusted LMWH with concomitant warfarin. Either UFH or LMWH should be maintained until the INR is between 2.0 and 3.0 for 2 consecutive days. Strong consideration should be given, however, to continuing LMWH for at least the first 3 to 6 months of long-term anticoagulation. This recommendation is based on warfarin’s high reported failure rate in cancer patients and on evidence that LMWHs are more efficacious in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding. LMWHs may also provide a mortality advantage in this popula-
tion. Therefore, LMWH can be used alone to treat VTE in cancer patients, but since the cost of LMWH may not be covered by insurance providers, it may be more practical to bridge patients to warfarin (INR 2.0 to 3.0) indefinitely or until the cancer has resolved.

**SUMMARY**

Optimal dosing of LMWH has not yet been established for patients with morbid obesity or renal insufficiency or for pregnant women. Monitoring of anti-Xa levels may not be covered by insurance providers, it may be generally required to escalate and prolong anticoagulation in these special populations. Use of fondaparinux in these special populations has yet to be defined, given that there is currently no measure of its biologic activity. Cancer patients are at especially high risk of VTE and its complications and therefore generally require escalated and prolonged anticoagulation and more intense monitoring of therapy.

**REFERENCES**