Anticoagulation in special patient populations:

Are special dosing considerations required?

FRANKLIN MICHOTA, MD, AND GENO MERLI, MD

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/m^2), 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).

From the Section of Hospital Medicine, Department of General Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio (FM); and the Division of Internal Medicine, Jefferson Medical College, Thomas Jefferson University Hospital, Philadelphia, Pa. (GM).

Address: Franklin Michota, MD, Department of General Internal Medicine, E13, Cleveland Clinic Foundation, Cleveland, OH 44195; michotf@ccf.org.

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[1] 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.[2] These data suggest that weight-adjusted doses may be more appropriate than fixed doses for VTE prophylaxis in morbidly obese patients.

Scholten et al[3] 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.[4]

It should be noted that heparin activity correlates with LMWH dose even in nonobese patients. Using data from the MEDENOX trial,[5] 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

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

Enoxaparin 1 mg/kg every 12 hours	0.6–1.0 IU/mL
Enoxaparin 1.5 mg/kg daily	1.0–1.5 IU/mL
Tinzaparin 175 IU/kg daily	0.85–1.0 IU/mL
Dalteparin 100 IU/kg every 12 hours	0.4–1.1 IU/mL
Dalteparin 200 IU/kg daily	1.0–2.0 IU/mL

* 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 al[7] 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,[8] 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/m^2 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.[9] 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.[13] 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.[14–16] Sanderink et al[17] 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 cutpoint 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.

TABLE 2
FDA dosing guidelines for enoxaparin in patients with renal insufficiency*

Prophylaxis in the medically ill patient
• Enoxaparin 30 mg daily
Inpatient treatment of DVT with or without PE
• Enoxaparin 1 mg/kg daily
Outpatient treatment of DVT without PE
• Enoxaparin 1 mg/kg daily

*Creatinine clearance of less than 30 mL/min
DVT = deep vein thrombosis; PE = pulmonary embolism

PREGNANT WOMEN

The incidence of DVT in pregnant women is about six times the incidence in nonpregnant women.[18] 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.[19,20] 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.[21,22]

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,[23] 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)**.[23] 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 thrombotic events and a personal history of VTE, we

TABLE 3
Dosing regimens for LMWHs in pregnancy

Prophylactic LMWH
- Dalteparin 5,000 IU or enoxaparin 40 mg daily

Intermediate-dose prophylactic LMWH
- Dalteparin 5,000 IU or enoxaparin 40 mg twice daily

Adjusted-dose LMWH titrated via anti-Xa monitoring
- Dalteparin 100 IU/kg or enoxaparin 1 mg/kg twice daily

Postpartum prophylaxis
- Warfarin for 4 to 6 weeks to a target INR of 2.0 to 3.0 with initial UFH or LMWH overlap until INR is 2.0–3.0. Warfarin can be used safely in breast-feeding women.

Adapted from recommendations in reference 23.

LMWH = low-molecular-weight heparin; INR = international normalized ratio; UFH = unfractionated heparin

recommend intermediate-dose LMWH (see **Table 3**) plus postpartum prophylaxis. Similarly, women with antithrombin deficiency, prothrombin gene mutation, or factor V Leiden mutation (compound heterozygotes or homozygotes) with a history of VTE should receive intermediate-dose LMWH during pregnancy as well as postpartum prophylaxis for 4 to 6 weeks. For a patient with multiple episodes of VTE receiving long-term anticoagulation with warfarin, the warfarin should be discontinued and full weight-adjusted LMWH started. In the postpartum period, crossover to warfarin is recommended until an INR of 2.0 to 3.0 is achieved.

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 abruption 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 abruption. 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 with warfarin crossover 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 1.2 IU/mL.[23] 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.

TABLE 4
VTE prophylaxis and treatment in cancer patients

VTE prophylaxis for the surgical patient

High-risk patient
- UFH 5,000 U 2 hr preoperatively, then every 8 hr
- Enoxaparin 40 mg or dalteparin 5,000 IU daily

Very-high-risk patient
- IPC sleeve ± gradient elastic stockings *plus*
  —UFH 5,000 U 2 hr preoperatively, then every 8 hr
  —Enoxaparin 40 mg or dalteparin 5,000 IU daily
- Extended prophylaxis (in selected high-risk patients):
  —Enoxaparin 40 mg daily for 1 month

VTE prophylaxis for the medical patient
- UFH 5,000 U every 8 hr
- Enoxaparin 40 mg daily
- Dalteparin 5,000 IU daily
- Fondaparinux 2.5 mg daily

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*
- LMWH (enoxaparin 1 mg/kg every 12 hr, or tinzaparin 175 IU/kg daily) with concomitant warfarin*
- LMWH alone (dalteparin 200 IU/kg once daily for 1 month followed by 150 IU/kg once daily for 5 months, or enoxaparin 1.5 mg/kg once daily for 6 months)†

Adapted from recommendations in references 32 and 39.

*Continue warfarin indefinitely or until cancer has resolved.

†Although indefinite anticoagulation therapy is recommended in cancer patients, use of LMWH beyond 6 months has not been studied in clinical trials.

VTE = venous thromboembolism; UFH = unfractionated heparin; IPC = intermittent pneumatic compression; aPTT = activated partial thromboplastin time; LMWH = low-molecular-weight heparin

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.

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.[24,25] 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

of anticoagulation, and have a poorer prognosis.[26,27] For these reasons, cancer patients should be viewed as being at especially high risk for VTE complications and in need of more intense anticoagulation monitoring.

The underlying etiology for cancer's prothrombotic tendency is the impact that malignant disease has on Virchow's triad of stasis, intimal injury, and hypercoagulability. The contributory effect of stasis to VTE in cancer patients stems from abnormalities in blood flow, immobility as a result of cancer-related debility, and compression of blood flow or invasion of vessels by expanding tumor growth. Vascular endothelium also plays a major role, with changes seen in concentrations of thrombosis-modulating factors such as von Willebrand factor, soluble thrombomodulin, soluble E selectin, and inflammatory cytokines.[28] In cancer, tumor cells can activate the coagulation system directly, through interactions with platelets, clotting factors, and the fibrinolytic system, to generate a hypercoagulable state.[29] In addition, two extrinsic causes of hypercoagulability are cancer surgery and chemotherapy. Approximately 60% of cancer patients undergo some sort of surgery, with all its attendant risks for VTE. Chemotherapies such as cisplatin, etoposide, medroxyprogesterone, and tamoxifen, as well as the vascular catheters through which these agents are delivered, have all been reported to increase the risk of thrombosis.[30,31]

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)**.[32] 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.[32] Most cancer patients undergoing surgery will be in the very-high-risk group, ie, 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 5%, respectively.[32] Given these high rates of significant VTE events, all cancer patients undergoing major surgery should receive aggressive VTE prophylaxis, as represented in the regimens of choice detailed in **Table 4**. Once the patient is ambulatory, intermittent pneumatic compression sleeves (see **Table 4**) may be removed, but pharmacologic prophylaxis should be maintained at least until hospital discharge.[32]

Bergqvist et al[33] conducted a placebo-controlled study of extended out-of-hospital VTE prophylaxis with LMWH for 1 month following major abdominal or pelvic cancer surgery. The incidence of postdischarge VTE was 12.8% in the placebo group and 4.8% in LMWH group (P = .02). In new consensus guidelines from the American College of Chest Physicians,[32] extended out-of-hospital VTE prophylaxis with LMWH is recommended in selected high-risk general surgery patients **(Table 4)**. Cancer patients undergoing surgery should be strongly considered for such extended VTE prophylaxis.

Prophylaxis in medical patients with cancer

The hospitalized medical patient with cancer is also at increased risk for VTE. The overall reported prevalence of VTE in medical patients is about 10% to 20% in the absence of prophylaxis.[32] In a prospective placebo-controlled trial using bilateral leg venographic end points, Samama et al[34] documented a 15% incidence of DVT in the placebo group, with 5% of events being proximal in origin. In univariate analysis, cancer conferred a relative risk of 1.74 (95% CI, 1.13 to 2.68) for development of thrombotic events. A multivariate logistic regression model showed that the odds ratio for VTE in cancer patients was 1.62 (95% CI, 0.93 to 2.75).[35]

The recommendation for VTE prophylaxis in hospitalized medical patients with cancer is either escalated UFH 5,000 U every 8 hours or LMWH (enoxaparin 40 mg or dalteparin 5,000 IU) once daily until discharge **(Table 4)**. Recently the pentasaccharide fondaparinux (2.5 mg daily) was also shown to be effective and safe, relative to placebo, for prevention of VTE in 849 acutely ill medical patients.[36] The degree to which cancer patients were represented in this study has not yet been reported, but fondaparinux may be a reasonable alternative in this setting, based on proven efficacy in other high-risk groups, such as arthroplasty patients.

The optimal duration of prophylaxis in the medically ill patient is currently being studied, yet data from surgical trials suggest that extended out-of-hospital prophylaxis may also be appropriate for this patient group.

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.[37,38] 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.[38,39] LMWHs may also provide a mortality advantage in this popula-

tion.[39] 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 be warranted and helpful in all of these special groups. 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

1. **Frederiksen SG, Hedenbro JL, Norgren L.** Enoxaparin effect depends on body-weight and current doses may be inadequate in obese patients. Br J Surg 2003; 90:547–548.
2. **Priglinger U, Delle Karth G, Geppert A, et al.** Prophylactic anticoagulation with enoxaparin: is the subcutaneous route appropriate in the critically ill? Crit Care Med 2003; 31:1405–1409.
3. **Scholten DJ, Hoedema RM, Scholten SE.** A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obes Surg 2002; 12:19–24.
4. **Kalfarentzos F, Stavropoulou F, Yarmenitis S, et al.** Prophylaxis of venous thromboembolism using two different doses of low-molecular-weight heparin (nadroparin) in bariatric surgery: a prospective randomized trial. Obes Surg 2001; 11:670–676.
5. **Desjardins L, Bara L, Boutitie F, et al.** Correlation of plasma coagulation parameters with thromboprophylaxis, patient characteristics, and outcome in the MEDENOX study. Arch Pathol Lab Med 2004; 128:519–526.
6. **Hainer JW, Barrett JS, Assaid CA, et al.** Dosing in heavyweight/obese patients with the LMWH tinzaparin: a pharmacodynamic study. Thromb Haemost 2002; 87:817–823.
7. **Shepherd MF, Rosborough TK, Schwartz ML.** Heparin thromboprophylaxis in gastric bypass surgery. Obes Surg 2003; 13:249–253.
8. **Montalescot G, Polle V, Collet JP, et al.** Low molecular weight heparin after mechanical heart valve replacement. Circulation 2000; 101:1083–1086.
9. **Spinler SA, Inverso SM, Cohen M, et al.** Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: analysis from the ESSENCE and TIMI 11B studies. Am Heart J 2003; 146:33–41.
10. **Wilson SJ, Wilbur K, Burton E, Anderson DR.** Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. Haemostasis 2001; 31:42–48.
11. **Smith J, Canton EM.** Weight-based administration of dalteparin in obese patients. Am J Health Syst Pharm 2003; 60:683–687.
12. **Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al.** Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin versus enoxaparin. Chest 2004; 125:856–863.
13. **Hirsh J, Raschke R.** Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):188S–203S.
14. **Cadroy Y, Pourrat J, Bladre M, et al.** Delayed elimination of enoxaparin in patients with chronic renal insufficiency. Thromb Res 1991; 63:385–390.
15. **Becker RC, Spencer FA, Gibson M, et al.** Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. Am Heart J 2002; 143:753–759.
16. **Chow SL, Zammit K, West K, et al.** Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. J Clin Pharmacol 2003; 43:586–590.
17. **Sanderink G, Le Liboux A, Jariwala N, et al.** The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther 2002; 72:308–318.
18. **Eldor A.** Unexplored territories in the nonsurgical patient: a look at pregnancy. Semin Hematol 2001; 38(2 Suppl 5):39–48.
19. **Greer IA.** Epidemiology, risk factors and prophylaxis of venous thromboembolism in obstetrics and gynaecology. Baillieres Clin Obstet Gynaecol 1997; 11:403–430.
20. **Koonin L, Atrash H, Lawson H, et al.** Maternal mortality surveillance, United States, 1979-1986. MMWR CDC Surveill Summ 1991; 40:1–13.
21. **Bonnar J.** Venous thromboembolism and pregnancy. Clin Obstet Gynaecol 1981; 8:455–473.
22. **Stirling Y, Woolf L, North W, et al.** Hemostasis in normal pregnancy. Thromb Haemost 1984; 52:176–182.
23. **Bates SM, Greer IA, Hirsh J, Ginsberg JS.** Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):627S–644S.
24. **Johnson MJ, Sproule MW, Paul J.** The prevalence and associated variables of deep venous thrombosis in patients with advanced cancer. Clin Oncol (R Coll Radiol) 1999; 11:105–110.
25. **Rickles FR, Levine MN.** Venous thromboembolism in malignancy and malignancy in venous thromboembolism. Haemostasis 1998; 28(Suppl 3):43–49.
26. **Levitan N, Dowlati A, Remick SC, et al.** Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore) 1999; 78:285–291.
27. **Bona RD, Hickey AD, Wallace DM.** Warfarin is safe as secondary prophylaxis in patients with cancer and a previous episode of venous thrombosis. Am J Clin Oncol 2000; 23:71–73.
28. **Lip GYH, Chin BS, Blann AD.** Cancer and the prothrombotic state. Lancet Oncol 2002; 3:27–34.
29. **Hara Y, Steiner M, Baldini MG.** Characterization of the platelet-aggregating activity of tumor cells. Cancer Res 1980; 40:1217–1222.
30. **Levine MN, Gent M, Hirsh J, et al.** The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. N Engl J Med 1988; 318:404–407.
31. **Goodnough LT, Saito H, Manni A, et al.** Increased incidence of thromboembolism in stage IV breast cancer patients treated with a five-drug chemotherapy regimen. Cancer 1984; 54:1264–1268.
32. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(Suppl 3):338S–400S.
33. **Bergqvist D, Agnelli G, Cohen AT, et al.** Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346:975–980.
34. **Samama MM, Cohen AT, Darmon JY, et al.** A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999; 341:793–800.
35. **Alikhan R, Cohen AT, Combe S, et al.** Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med 2004; 164:963–968.
36. **Cohen A, Davidson B, Gallus A, et al.** Fondaparinux for the prevention of VTE in acutely ill medical patients [abstract]. Blood 2003; 102:15a.
37. **Lensing AW, Prins MH, Davidson BL, Hirsh J.** Treatment of deep venous thrombosis with low-molecular-weight heparins. A meta-analysis. Arch Intern Med 1995; 155:601–607.
38. **Lee AY, Levine MN, Baker RI, et al.** Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146–153.
39. **Buller HR, Agnelli G, Hull RD, et al.** Antithrombotic therapy for venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(Suppl 3):401S–428S.