NCCN Guidelines® Insights

Cancer-Associated Venous Thromboembolic Disease, Version 1.2015

Featured Updates to the NCCN Guidelines

Michael B. Streiff, MD[1,*]; Bjorn Holmstrom, MD[2,*]; Aneel Ashrani, MD[3]; Paula L. Bockenstedt, MD[4]; Carolyn Chesney, MD[5]; Charles Eby, MD[6]; John Fanikos, RPH, MBA[7]; Randolph B. Fenninger, JD[8]; Annemarie E. Fogerty, MD[9]; Shuwei Gao, MD[10]; Samuel Z. Goldhaber, MD[7]; Paul Hendrie, MD[11]; Nicole Kuderer, MD, MS[11]; Alfred Lee, MD, PhD[12]; Jason T. Lee, MD[13]; Mirjana Lovrincevic, MD[14]; Michael M. Millenson, MD[15]; Anne T. Neff, MD[16]; Thomas L. Ortel, MD, PhD[17,*]; Rita Paschal, MD[18]; Sanford Shattil, MD[19]; Tanya Siddiqi, MD[20]; Kristi J. Smock, MD[21]; Gerald Soff, MD[22]; Tzu-Fei Wang, MD[23,*]; Gary C. Yee, PharmD[24]; Anaadriana Zakarija, MD[25]; Nicole McMillian, MS[26,*] and Anita M. Engh, PhD[26,*]

Abstract

The NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease outline strategies for treatment and prevention of venous thromboembolism (VTE) in adult patients with a diagnosis of cancer or for whom cancer is clinically suspected. VTE is a common complication in patients with cancer, which places them at greater risk for morbidity and mortality. Therefore, risk-appropriate prophylaxis is an essential component for the optimal care of inpatients and outpatients with cancer. Critical to meeting this goal is ensuring that patients get the most effective medication in the correct dose. Body weight has a significant impact on blood volume and drug clearance. Because obesity is a common health problem in industrialized societies, cancer care providers are increasingly likely to treat obese patients in their practice. Obesity is a risk factor common to VTE and many cancers, and may also impact the anticoagulant dose needed for safe and effective prophylaxis. These NCCN Guidelines Insights summarize the data supporting new dosing recommendations for VTE prophylaxis in obese patients with cancer. (J Natl Compr Canc Netw 2015;13:1079–1095)

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [2]Moffitt Cancer Center; [3]Mayo Clinic Cancer Center; [4]University of Michigan Comprehensive Cancer Center; [5]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [6]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [7]Dana-Farber/Brigham and Women's Cancer Center; [8]National Blood Clot Alliance; [9]Massachusetts General Hospital Cancer Center; [10]The University of Texas MD Anderson Cancer Center; [11]University of Washington/Seattle Cancer Care Alliance; [12]Yale Cancer Center/Smilow Cancer Hospital; [13]Stanford Cancer Institute; [14]Roswell Park Cancer Institute; [15]Fox Chase Cancer Center; [16]Vanderbilt-Ingram Cancer Center; [17]Duke Cancer Institute; [18]University of Alabama at Birmingham Comprehensive Cancer Center; [19]UC San Diego Moores Cancer Center; [20]City of Hope Comprehensive Cancer Center; [21]Huntsman Cancer Institute at the University of Utah; [22]Memorial Sloan Kettering Cancer Center; [23]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [24]Fred & Pamela Buffett Cancer Center; [25]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; and [26]National Comprehensive Cancer Network

*Provided content development and/or authorship assistance.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease

Disclosure of Relevant Financial Relationships

Editor:

Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

CE Planners:

Deborah J. Moonan, RN, BSN, Director, Continuing Education, NCCN, has disclosed that she has no relevant financial relationships.

Ann Gianola, MA, Manager, Continuing Education Accreditation & Program Operations, NCCN, has disclosed that she has no relevant financial relationships.

Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

Rashmi Kumar, PhD, Senior Manager, Clinical Content, NCCN, has disclosed that she has no relevant financial relationships.

Individuals Who Provided Content Development and/or Authorship Assistance:

Michael B. Streiff, MD, has disclosed that he receives consulting fees from BiO2 Medical Inc.; CSL Behring; Janssen Pharmaceuticals, Inc. He receives research support from Daiichi Sankyo, Inc., Janssen Pharmaceuticals, Inc., Portola Pharmaceuticals, Inc.
Bjorn Holmstrom, MD, has disclosed that he has no relevant financial relationships.
Thomas L. Ortel, MD, PhD, has disclosed that he is a principal investigator for Daiichi Sankyo Company, Eisai Inc., GlaxoSmithKline, and Pfizer Inc.; is an advisory board member for Daiichi Sankyo Company; and receives consultant fees/honoraria from Instrumentation Laboratory.
Tzu-Fei Wang, MD, has disclosed that she has no relevant financial relationships.
Nicole R. McMillian, MS, Guidelines Coordinator, NCCN, has disclosed that she has no relevant financial relationships.
Anita M. Engh, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

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INPATIENT/OUTPATIENT PROPHYLACTIC ANTICOAGULATION TREATMENT[1,2,3]

Agent	Standard Dosing	Obesity Dosing (BMI ≥40 kg/m^2)[4]
LMWH[5]		
• Dalteparin	5,000 units SC daily (category 1 for inpatient)	Consider 7500 units SC daily (limited data)
• Enoxaparin	40 mg SC daily (category 1 for inpatient)	Consider 40 mg SC every 12 hours
Fondaparinux[6]	2.5 mg SC daily (category 1 for inpatient)	Consider 5 mg SC daily (limited data)
UFH	5,000 units SC every 8–12 hours (category 1 for inpatient)	Consider 7500 units SC every 8 hours
Aspirin	81–325 mg daily (for low-risk multiple myeloma outpatients only)[7]	
Warfarin	Adjusted to INR 2–3[8]	

For Diagnosis and Treatment of HIT See (HIT-1)

[1]Agent selection based on: Renal failure (C_{cr} <30 mL/min), FDA approval, cost, ease of administration, monitoring, and ability to reverse anticoagulation.
[2]Follow institutional standard operating procedures (SOPs) for dosing schedules. If no SOPs then use the American College of Chest Physicians (ACCP) recommendations. (Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e195S-226S; and Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e24S-43S [www.chestjournal.org]).
[3]Following initiation of heparin: Hemoglobin, hematocrit, and platelet count every 2–3 days up to at least day 14 and every two weeks thereafter or as clinically indicated.
[4]Given the impact of renal insufficiency on clearance of enoxaparin and fondaparinux, UFH or dalteparin are recommended for obese patients with severe renal impairment (C_{cr} <30 ml/min).
[5]LMWHs should be used with caution in patients with renal dysfunction. Dose adjustments and Anti-Xa monitoring may be required. Follow package insert for renal dysfunction ~~and body weight-based~~ dosing.
[6]Fondaparinux is contraindicated in patients with creatinine clearance <30 mL/min. Use with caution in patients with moderate renal insufficiency (creatinine clearance 30–50 mL/min), weight <50 kg, or age >75 years.
[7]Use only for lower risk multiple myeloma outpatients with one or fewer individual or myeloma risk factors (See VTE Risk Factors in Cancer Patients [VTE-A]).
[8]Warfarin (INR 2–3) or LMWH (eg, enoxaparin 40 mg SC every 24 hours) are prophylaxis options for select high-risk myeloma outpatients receiving highly thrombotic anti-angiogenic therapy (ie, multiple myeloma patients receiving thalidomide/lenalidomide in combination with high-dose dexamethasone [≥480 mg per month] or doxorubicin or multi-agent chemotherapy) or for myeloma patients with two or more individual or myeloma risk factors (See VTE Risk Factors in Cancer Patients [VTE-A]).

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VTE-C

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Venous thromboembolism (VTE) is a common and life-threatening condition in patients with cancer.[1,2] Results from large retrospective studies (N>10,000) indicate that VTE may occur in up to 19% of patients with cancer, depending on the tumor type.[1–3] The critical need for clinical practice guidelines focusing specifically on VTE in patients with cancer is underscored by studies showing underuse of VTE prophylaxis among these patients,[4–6] despite the strong association between VTE and cancer.[7–11]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cancer-Associated Venous Thromboembolic Disease outline strategies to prevent and treat VTE in adult patients with cancer, including medically ill or surgery inpatients and outpatients. These guidelines were developed and are updated annually by the NCCN Cancer-Associated Venous Thromboembolic Disease Panel, an interdisciplinary group of representatives from NCCN

Member Institutions, including specialists in hematology and hematology/oncology, surgery and surgical oncology, cardiology, internal medicine, pharmacology, and pharmacy. In the guidelines, VTE is broadly defined to include deep venous thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis, and venous thrombosis in other areas of the vasculature. Based on assessment of VTE risk and in the absence of contraindications to anticoagulation, the guidelines recommend pharmacologic prophylaxis for medical and surgical patients with cancer during hospitalization (category 1 recommendation) and in some cases after discharge (see VTE-1 and VTE-2, in the full version of these guidelines at NCCN.org). Obesity is common among patients with cancer and increases the risk of VTE[12,13]; therefore, these NCCN Guidelines Insights focus on a notable addition to the 2015 NCCN Cancer-Associated Venous Thromboembolic Disease Guidelines: prophylactic anticoagulant dosing for patients with obesity.

Obesity and Cancer

Obesity is considered an epidemic in the United States, affecting at least one-third of the adult population,[12–14] with rates steadily increasing.[14–16] High body mass index (BMI) is a risk factor for cancer,[17–19] and is more prevalent among patients with cancer compared with the general population. Various estimates have been reported for the fraction of cancer cases attributable to obesity, ranging from 3.6% of new cancer cases worldwide to 20% of all cancer cases.[20,21] Obesity is strongly associated with certain types of cancer, including 8 recognized by the World Cancer Research Fund: esophageal adenocarcinoma and colorectal, kidney, pancreatic, gallbladder, postmenopausal breast, endometrial, and ovarian cancers.[21–24] The associations between these cancers and obesity are supported by a vast body of literature, including large meta-analyses showing statistically significant correlations between cancer risk and increasing BMI.[30] Primary reports and meta-analyses support that high BMI also increases the risk of aggressive prostate cancer, liver cancer, thyroid cancer, leukemia, malignant melanoma, and non-Hodgkin's lymphoma.[19,25–31] Oncologists are likely to encounter many obese and overweight patients, and these patients may be particularly difficult to treat, requiring closer monitoring and more interventions. Practitioners need to be aware of key considerations for patients with high BMI when determining treatment choice, dosing, and supportive care.

Effect of Obesity and Cancer on Risk of VTE

One important consideration for supportive care is that obesity and cancer both increase the risk of VTE. The presence of cancer increases the VTE risk by 4- to 7-fold, and may cause up to 20% of VTE cases.[32,33] The association between obesity and VTE is also fairly well established. High BMI (≥35 kg/m^2) is included in the calculation of the Khorana score, a metric for assessing risk of VTE in patients with cancer.[34] A recent population-based study (N>30,000) in the United States showed that in participants aged 45 years and older, obesity (BMI≥30 kg/m^2) was the variable most strongly correlated with VTE.[35] Other notably large studies reporting increased rates of VTE in patients with high BMI include a population-based study in Denmark (N>80,000),[36] analysis of a cohort (N>15,000) from the Atherosclerosis Risk in Communities study,[37] and a prospective study (N>30,000) using the Reasons for Geographic and Racial Differences in Stroke cohort.[38] Likewise, obesity rates are higher among patients diagnosed with VTE than in the general population.[39–41] Interestingly, even among patients with cancer, the risk of VTE may be higher in those who are obese.[42] A recently reported analysis of 6,710,066 hospitalizations of US adults found that obesity and metastatic cancer were significantly and independently associated with diagnosis of VTE on hospitalization, indicating that VTE risk would be significantly higher in patients with both conditions (obesity and cancer) relative to those with only one of these risk factors.[43]

Obesity and Perioperative VTE Risk

In addition to increasing the risk of VTE, high BMI also increases VTE risk in the perioperative setting. Across different types of surgery, including surgery for cancer treatment, BMI correlates with risk of complications, greater blood loss, increased operating times, anastomosis leakage, and longer hospital stays.[44,45] A number of analyses, some based on very large patient populations (>2 million shoulder arthroplasties; >20,000 total knee arthroplasties, >26,000 total joint arthroplasties), have shown that obesity increases

risk of VTE during orthopedic surgeries.[46–48] Several large retrospective studies have shown that, for patients undergoing bariatric surgery, the risk of VTE increases with increasing BMI,[49,50] a correlation that may be attributed to operating time increasing with BMI.[51] Large studies including patients with cancer have shown that obesity is an independent risk factor for portomesenteric VTE in patients receiving major colon and rectal surgery,[52] and may increase the risk of VTE associated with central venous catheters or peripherally inserted central catheters used for chemotherapy delivery.[53–55] The increased risk of perioperative VTE in obese patients means that safe and appropriate VTE prophylaxis may be critical for obese patients with cancer undergoing surgery. Careful determination of the prophylactic anticoagulant dose is especially important in obese patients because of the increased operating times and blood loss.

Adjusting Dosing for Obese Patients

Studies aimed at determining the best approach to dosing in obese patients have produced a variety of results depending on the indication and medication tested.[56–58] Obesity can potentially affect pharmacokinetics and pharmacodynamics though a variety of physiologic mechanisms, the net result of which could increase or decrease the dose effect. The impact of obesity on the effective dose depends on the agent-specific mechanism of action and pathways of metabolism and elimination. Although for some drugs standard dosing is safe and effective in obese patients, many agents require linear weight-based dose adjustments, and some may require more detailed pharmacokinetic characterization or biomarker measurements to determine the optimal dose for obese patients. One systematic review of chemotherapy dosing indicated that the need for weight-based dose adjustment varies by agent,[59] and the ASCO Clinical Practice Guidelines, based on a systematic literature review, recommend weight-based dosing (using actual body weight) for most cytotoxic chemotherapy agents, with a few notable exceptions.[60]

Weight-Based Anticoagulant Dosing in Patients With High BMI

The development of evidence-based recommendations is hampered by the lack of randomized controlled trials (RCTs) in obese patients comparing standard anticoagulant dosing versus weight-based dosing or higher fixed dosing. However, a number of studies have reported data from obese patients receiving pharmacologic VTE prophylaxis. These reports show that, although patients with high BMI benefit from VTE prophylaxis, VTE rates in patients receiving prophylactic anticoagulation are higher for obese compared with patients with a lower BMI.[61–66] These data suggest that patients with high BMI may need higher anticoagulant doses to prevent VTE. Indeed, a meta-analysis of bariatric surgery patients receiving prophylactic heparin products (unfractionated heparin [UFH] and low-molecular-weight heparin [LMWH]) showed that weight-adjusted doses were associated with lower VTE rates compared with standard fixed dosing.[67]

Comparing efficacy of anticoagulant prophylactic dosing regimens can be difficult because reliable measurement of VTE rates requires large sample sizes and long follow-up. Anti–factor Xa (anti-FXa) level, a measure of anticoagulation, has often been used as a surrogate measure of anticoagulant efficacy and safety.[68] These data must be interpreted with caution, however, because anti-FXa levels have not been demonstrated conclusively to be associated with clinical events.[68]

For the 2015 update to the NCCN Guidelines for Cancer-Associated VTE, the panel added dosing recommendations for obese patients receiving prophylaxis with dalteparin, enoxaparin, UFH, and fondaparinux (see VTE-C, page 1081). Appendices 1 through 4 summarize the key studies providing pharmacodynamic, efficacy, and safety data from obese patients receiving these agents for VTE prophylaxis.

Dalteparin

Studies reporting pharmacodynamic, efficacy, or safety data from obese patients treated with prophylactic dalteparin are summarized in Appendix 1. Two RCTs included patients with high BMI treated with prophylactic dalteparin. The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients (PREVENT) trial compared prophylactic dalteparin with placebo in 3708 medically ill hospitalized patients with at least one VTE risk factor.[63] A retrospective subgroup analysis of patients with high BMI (n=1118, most with a BMI of 30.0–34.9 kg/m^2) showed that the standard prophylactic dalteparin dosage, 5000 U/d, improved outcomes rel-

ative to placebo without increasing bleeding event rates.[63] Interestingly, the beneficial effect of dalteparin prophylaxis was apparent across all BMI-based subgroups except for the group with BMI greater than 40 kg/m^2, hinting that standard dosing may not be sufficient for morbidly obese patients. Agnelli et al[61] reported similar results from their subgroup analysis of an RCT testing VTE prophylaxis with dalteparin (vs fondaparinux) in high-risk patients undergoing abdominal surgery: high BMI was associated with increased VTE rates in both treatment groups, but did not appear correlated with bleeding rates.[61] Patients in the dalteparin arm received 2500 U before surgery and 12 hours after surgery, followed by 5000 U once daily; results therefore support that standard dosing may be insufficient for VTE prophylaxis in the obese. In an analysis of 735 patients undergoing bariatric surgery,[69] prophylaxis with dalteparin at 2500 U immediately before surgery followed by 5000 U/d (for ≥1 week) provided protection against VTE even after long-term follow-up (0% after ≥6 months), with few patients (<0.5%) having bleeds in the immediate postoperative period. The low VTE rate reported by Magee et al[69] may be due to the small number of patients with extreme obesity in the study population, and that only symptomatic VTE was recorded, whereas the previously described RCTs used prospective duplex ultrasound surveillance.[61,63]

A retrospective analysis by Simoneau et al[70] showed that dalteparin at 7500 U/d may be an appropriate dose for many obese patients undergoing bariatric surgery: more than 60% had anti-FXa levels within the target range, and none experienced VTE. Bleeding occurred in 2.2% of obese patients, and did not appear correlated with anti-FXa level. Although the data are limited, the NCCN panel recommends considering dalteparin at 7500 U subcutaneous daily for VTE prophylaxis in patients with a BMI of 40 kg/m^2 or greater (see VTE-C, page 1081).

Enoxaparin

Several studies have compared prophylactic fixed-dose enoxaparin regimens in obese patients, primarily in the context of bariatric surgery (Appendix 2).[65,71–74] Scholten et al[71] conducted a large retrospective study in patients with extreme obesity receiving enoxaparin before bariatric surgery and then every 12 hours until discharge or ambulation. Results showed that 40 mg twice daily was associated with lower VTE rates during hospitalization and the 6 months following discharge than 30 mg twice daily, without increasing the incidence of bleeding. It is important to note that there was a trend toward higher BMI, higher male/female ratio, longer hospital stay, and longer procedure duration among patients in the 30-mg twice-daily group. The multicenter retrospective PROBE study of patients undergoing bariatric surgery showed that various enoxaparin 40-mg regimens were associated with lower VTE rates compared with the 30-mg regimens but may have increased the risk of severe bleeds.[72] A retrospective analysis by Raftopoulos et al[65] showed that for bariatric surgery patients receiving 30 mg of enoxaparin twice daily while hospitalized, rates of VTE and major bleeds were significantly reduced by a course of 40-mg once-daily dosing for 10 days after discharge. A large retrospective study by Wang et al[66] found that for extremely obese (BMI>40 kg/m^2) hospitalized patients, VTE rates were significantly lower with high-dose versus low-dose enoxaparin (40 mg twice daily vs once daily) or UFH.[66] Based on review of these findings, the NCCN Cancer-Associated VTE Panel recommends considering more frequent prophylactic enoxaparin dosing for obese patients (BMI≥40 kg/m^2): 40 mg every 12 hours (rather than once daily; see VTE-C, page 1081).

Anti-FXa data from multiple studies suggest that higher doses may be needed for effective VTE prophylaxis in obese patients receiving enoxaparin after bariatric surgery (Appendix 2). A prospective study reported by Rowan et al[73] showed that increasing the enoxaparin twice-daily dose from 30 to 40 mg increased the percentage of patients with anti-FXa levels within the target range. Nonetheless, therapeutic anti-FXa levels were achieved by fewer than 50% of patients who received 40-mg (twice daily) dosing, a finding corroborated by Steele et al,[75] supporting the conclusion that 40 mg every 12 hours may not be sufficient for all obese patients. A prospective study by Simone et al[74] showed that increasing enoxaparin from 40 to 60 mg twice daily reduced the proportion of patients with subtherapeutic anti-FXa levels from 44% to 0%, but also increased the proportion of patients with supratherapeutic levels from 0% to 57%. These findings indicate that it may be difficult to identify a fixed twice-daily dose that safely prevents VTE in all obese patients. Indeed, a more recent study by Celik et al[76] showed that body weight was an independent predictor of anti-FXa levels in

patients receiving enoxaparin at 40 mg twice daily for VTE prophylaxis after bariatric surgery. The 40-mg twice-daily dosage appeared optimal for the subgroup of patients weighing 110 to 150 kg, with 94% of these patients having anti-FXa levels in the target range. Patients with weights above or below this range tended to have anti-FXa levels that were subtherapeutic or supratherapeutic, respectively, indicating that weight-based dosing may be a better approach to achieve anti-FXa levels in the target range.

Several studies have tested weight-based enoxaparin dosing for VTE prophylaxis in obese patients (Appendix 2).[64,77–79] These studies show that weight-based enoxaparin dosing results in anti-FXa levels that are not correlated with weight or BMI.[64,77,79] Moreover, the percentage of patients achieving target anti-FXa levels was higher (>80%) with enoxaparin at 0.5 mg/kg compared with previously published fixed-dose regimens (described earlier).[64,78,79] In a prospective study of hospitalized, medically ill patients with extreme obesity (BMI≥40 kg/m^2) and at least one VTE risk factor, Freeman et al[79] compared 40-mg daily fixed dosing with 2 weight-based daily dosing regimens: 0.4 and 0.5 mg/kg. They showed that 0.5 mg/kg daily resulted in a significantly higher percentage of patients achieving target anti-FXa levels compared with the other 2 regimens. No symptomatic VTE or adverse events were observed, indicating that dose capping was not necessary up to the highest dose tested (130 mg/d). The 2015 NCCN Cancer-Associated VTE Guidelines update does not include weight-based enoxaparin dosing for VTE prophylaxis in obese patients because larger comparative trials are needed to determine whether this dosing regimen translates into lower event rates.

Two studies tested BMI-based enoxaparin dosing for VTE prophylaxis,[80,81] both in patients undergoing bariatric surgery (Appendix 2). Results from an open-label prospective trial reported by Borkgren-Okonek et al[81] showed that postoperative twice-daily enoxaparin dosing based on BMI (40 mg/60 mg for BMI ≤50/>50 kg/m^2) resulted in therapeutic anti-FXa levels in most patients (74%) and across the wide range of BMI (36–82 kg/m^2) in the sample population. Dosing was adjusted for anti-FXa levels outside the target range, resulting in a low rate of VTE (0.45%) and major bleeding in 2.2% of patients (>1-month follow-up). Singh et al[80] conducted a retrospective analysis of patients receiving twice-daily prophylactic enoxaparin doses ranging from 30 to 60 mg across 4 BMI-based subgroups. Remarkably, no symptomatic VTE was observed during the minimum 2-year follow-up. Significant bleeding occurred in 2.9% of patients, but was not correlated with higher doses. Although these studies provide preliminary data indicating that BMI-based dosing may be more effective for obese patients than fixed dosing, further evidence is needed to support this approach. The 2015 NCCN Cancer-Associated VTE Guidelines update therefore does not include BMI-based dosing for prophylactic enoxaparin.

Unfractionated Heparin

Bariatric surgery studies provide most of the data on VTE prophylaxis with UFH in obese patients (Appendix 3).[66,82,83] In these studies UFH is usually administered at 5000 U before surgery and/or 2 to 4 times per day after surgery. Several studies have tested higher doses in patients with extreme obesity.[66,84,85] Shepherd et al[84] reported a prospective series of 245 hospitalized medical and surgical patients, including 25% with a BMI greater than 35 kg/m^2 (BMI range, 14–71 kg/m^2; weight range, 34–193 kg), administered UFH twice-daily dosing adjusted to achieve therapeutic anti-FXa levels. This approach resulted in doses ranging from 3000 to 19,000 U in the population studied, and the equation that best predicted therapeutic dose included both patient height and weight. The derived equation was then used to determine initial UFH prophylactic dose for patients receiving bariatric surgery (N=700). The resultant VTE rate was notably low (0.4%, all nonfatal), and the bleed rate was similar to that seen in previous standard-dosing studies, even though many patients received doses much higher than 5000 U. The efficacy and safety of higher UFH doses in obese patients was corroborated by low rates of VTE and bleeding reported by Miller and Rovito[85] in their retrospective analysis of bariatric surgery patients who received prophylactic UFH every 8 hours at a BMI-dependent dose: 7500 U for BMI greater than 50 kg/m^2; 5000 U for BMI of 50 kg/m^2 or less. As described earlier, a much larger and more recent study by Wang et al[66] showed that using higher UFH/enoxaparin prophylactic dosing (UFH, 7500 U every 8 hours vs 5000 U 2 to 3 times per day; Appendix 2) in hospitalized obese patients (BMI≥40 kg/m^2) significantly reduced VTE without increasing bleeding. These

data support the NCCN Cancer-Associated VTE Panel's recommendation to consider using 7500 U every 8 hours in obese patients (BMI≥40 kg/m^2) receiving UFH for VTE prophylaxis (see VTE-C, page 1081.)

Fondaparinux

Limited data are available regarding fondaparinux dosing for VTE prophylaxis in patients with high BMI, although several studies have used the standard prophylaxis dose (2.5 mg/d) in hospitalized obese patients (Appendix 4).[61,86,87] Agnelli et al[61] reported results from an RCT in patients at high risk for VTE undergoing abdominal surgery, including more than 300 patients with high BMI (>30 kg/m^2 for women, >28.6 kg/m^2 for men). They found that a high BMI was associated with an increased risk of VTE, suggesting that extremely obese patients may need higher than standard fondaparinux doses for effective VTE prophylaxis. A more recent retrospective study by Martinez et al[87] provides additional evidence that standard fondaparinux VTE prophylaxis doses may be inadequate in obese patients (BMI≥40 kg/m^2): only 43% had anti-FXa levels within the therapeutic range, whereas 47% had subtherapeutic levels. Moreover, low anti-FXa was associated with higher BMI within the obese patient population tested. Steele et al[75] tested fondaparinux at 5 mg/d for thromboprophylaxis following bariatric surgery and found that this higher dose resulted in a higher proportion of patients (74%) achieving anti-FXa levels in the target range. Moreover, VTE only occurred in 2.2% of patients, and all these events were asymptomatic. This higher fondaparinux dose also had an acceptable safety profile, with only 4% of patients developing minor bleeds. Based on this study, the 2015 NCCN Cancer-Associated VTE Guidelines update recommends considering 5 mg/d in obese patients (BMI≥40 kg/m^2) receiving VTE prophylaxis with fondaparinux, acknowledging that supporting data are limited (see VTE-C, page 1081).

Renal Insufficiency and Anticoagulant Dosing in Obese Patients

Chronic kidney disease and renal insufficiency are associated with obesity [88–92] and with an increased risk of thromboembolic events.[93,94] Renal insufficiency is common in patients with VTE, with 52% having a creatinine clearance (C_{Cr}) of less than 90 mL/min.[95] In patients treated with anticoagulants, particularly LMWH and fondaparinux, renal insufficiency is associated with anti-FXa levels above the therapeutic range and poorer safety and efficacy outcomes.[96–99] For the obese with renal dysfunction, the safety of higher than standard prophylactic anticoagulant is unknown: many of the studies excluded patients with severe renal insufficiency (C_{Cr}<30 mL/min; Appendices 1–4), and whether any of the obese patients studied had mild or moderate renal insufficiency (C_{Cr}, 30–90 mL/min) is unclear. Given the impact of renal insufficiency on clearance of enoxaparin and fondaparinux, we would recommend use of UFH or dalteparin in obese patients with severe renal impairment (C_{Cr}<30 mL/min).

Conclusions

Anticoagulant dose adjustments may be critical for optimizing VTE prevention in obese patients with cancer, a population at increased risk for VTE. Based on evidence from the studies described earlier and the consensus of the NCCN panel, the 2015 NCCN Guidelines for Cancer-Associated VTE have been updated to include dose adjustments for obese patients receiving prophylaxis with dalteparin, enoxaparin, UFH, or fondaparinux. The panel agrees that prospective RCTs comparing efficacy and safety of different dosing regimens are needed to further support and optimize anticoagulant dose adjustment in obese patients.

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Instructions for Completion

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Posttest Questions

1. In the absence of contraindications to anticoagulation, VTE prophylaxis with an anticoagulant is recommended for patients with cancer in which of the following settings:
    1. During hospitalization for surgery
    2. During hospitalization for medical oncology treatment
    3. After discharge for all surgery and all medical oncology patients
    4. After discharge for all abdominal-pelvic cancer surgery patients and in some cases for medical oncology patients

   There is only one correct answer:
    a. 1
    b. 1 and 2
    c. 1–3
    d. 1, 2, and 4
2. True or false: Weight-based anticoagulant dosing is not recommended because it has not been tested in human subjects.
3. For pharmacologic thromboprophylaxis of overweight patients with cancer, the NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease recommends considering higher or more frequent dosing when prescribing which of the following anticoagulants?
    1. Dalteparin
    2. Enoxaparin
    3. Fondaparinux
    4. Unfractionated heparin
    5. Aspirin
    6. Warfarin

   There is only one correct answer:
    a. 1–4
    b. 1, 3, and 4
    c. 1, 3, 4, and 6
    d. 1–6

Appendix 1: Dalteparin for VTE Prophylaxis in Obese Patients

Study Design	Setting/ Inclusion Criteria	Obese, N	BMI[a], kg/m^2	Weight[a], kg	Dose and Regimen[b]	Anti-FXa [dose #][c]	VTE, n (%) [follow-up]	Major Bleeds, n (%) [follow-up]
Kucher et al,[63] 2005 Subgroup of PREVENT double-blind multicenter RCT	Medically ill; ≥1 VTE risk factor; Hospitalized >4 d; BMI ≥30/≥28.6 kg/m^2 in men/women; Creatinine ≤176.8 µmol/L	1118 A: 558 B: 560	34	91	A: 5000 U/d B: Placebo		2.8% vs 4.3%[e]; RR, 0.64; 95% CI, 0.32–1.28 [day 21]	0% vs 0.7%, *P*>.99 [day 21]
Agnelli et al,[61] 2005 Subgroup of double-blind multicenter RCT (vs fondaparinux)	Abdominal surgery >45 min; Age >60 y or >40 y with ≥1 VTE risk factor; BMI >30/>28.6 kg/m^2 in men/women; Creatinine ≤180 µmol/L	315	NR	NR	2500 U preop + 12 h postop, then 5000 U qd x 5–9 d		Risk increases with BMI[e]: OR, 1.08 per kg/m^2; 95% CI, 1.04–1.12 [30 ± 2 d]	Not correlated with BMI or C_{Cr}[e] [30 ± 2 d]
Magee et al, [69] 2010 Retrospective Single-institution	Bariatric surgery: laparoscopic	735	Median, 48 (35–103)	Median, 130 (77–298)	2500 U preop + 5000 U/d x ≥7 d postop		0 [≥6 mo]	3 (0.4%) [immediate postop period]
Simoneau et al, [70] 2010 Retrospective Single-institution	Bariatric surgery; BMI ≥40 kg/m^2 or >35 kg/m^2 with comorbidity; C_{Cr} ≥30 mL/min	135	57; ≥40 in 98%	149	7500 U qd starting day 2 postop	Below/met/above starget [4]: 25%/64%/11%[f]	0 [in hospital, ≥4 d]	3[g] (2.2%); NOT correlated with anti-FXa [in hospital, ≥4 d]

Abbreviations: BMI, body mass index; C_{Cr}, creatinine clearance rate; FXa, factor Xa; NR, not reported; OR, odds ratio; postop, postoperative; preop, preoperative; PREVENT, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients; RCT, randomized controlled trial; RR, risk ratio; VTE, venous thromboembolism.

[a]Mean (range), unless otherwise indicated.

[b]Dosing continued until discharge unless otherwise indicated.

[c]Anti-FXa levels measured at the peak, ≈4 h post-dose, with target range 0.2–0.5 U/mL, unless otherwise indicated. [dose #] is the dose after which the level was measured (ie, peak anti-FXa measured after the second dose would be annotated as [2]).

[d]Symptomatic VTE, fatal pulmonary embolism, sudden death, or asymptomatic proximal deep venous thrombosis.

[e]Includes entire population (all BMI, both treatment groups); patients with high BMI not analyzed separately.

[f]Blood samples collected at correct time in only 84 patients (62.2%).

[g]Severity was not reported for the 3 bleeding events observed: upper digestive hemorrhage, wound hematoma and paragastric hematoma.

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Appendix 2: Enoxaparin for VTE Prophylaxis in Obese Patients

Study Design	Setting/ Inclusion Criteria	Obese, N	BMI,[a] kg/m²	Weight,[a] kg	Dose and Regimen[b]	Anti-FXa [dose #][c]	VTE, n (%) [follow-up]	Major Bleeds, n (%) [follow-up]
Fixed Dosing								
Scholten,[71] 2002 Retrospective Single-institution	Bariatric surgery >2 h: 98% open; Age >40 y BMI >50 kg/m²	481 A: 92 B: 389	A: 52 B: 50	NR	A: 30 mg B: 40 mg preop + q12h postop		2 (2.2%) vs 0 [in hospital] 5 (5.4%) vs 2 (0.6%), *P*<.01 [6 mo]	1 (1.1%) vs 1 (0.3%) [6 mo]
Hamad & Choban,[72] 2005 Retrospective of PROBE multicenter study	Bariatric surgery: 85% open; 81.2% with ≥1 VTE risk factor	668 A, B: 100, 123 C, D, E: 84, 180, 180	50; >60 in 12.8%	NR	30 mg A: preop B: qd x 10 d postdischarge 40 mg postop C/D: qd x 2/5 d E: q12h x 3 d		7[d] A: 2 (2.0%) B: 3 (2.4%) C, D: 1 (1.1%), 0 E: 1 (0.5%) [mean, 10.5 mo]	A, C: 0, 0 B: 1 (0.8%) D: 3 (1.6%) E: 3 (1.6%) [mean, 10.5 mo]
Kothari et al,[100] 2007 Prospective Single-institution (vs UFH)	Bariatric surgery: laparoscopic	238	49	137	40 mg preop + bid postop		0 [30 d]	14 (5.9%) required transfusions; 4 (1.7%) required re-exploration [30 d]
Rowan et al,[73] 2008 Prospective Single-institution	Bariatric surgery: laparoscopic	52 A: 19 B: 33	A: 48 B: 49	A: 142 B: 136	A: 30 mg B: 40 mg Some preop + all q12h postop	Met target [1,3]: 0 vs 31% (*P*=.01), 9% vs 42% (*P*=.16) Increased with dose (*P*<.05)	NR	NR
Simone et al,[74] 2008 Prospective Single-institution	Bariatric surgery: laparoscopic	40 A: 24 B: 16	A: 49 B: 47	A: 135 B: 127	A: 40 mg B: 60 mg q12h postop	Below target [3]: 44% vs 0% Above target [3]: 0% vs 57%	NR	1 (2.5%) vs 0 [in hospital]
Raftopoulos et al,[65] 2008 Retrospective Single-institution	Bariatric surgery: >90% laparoscopic	308 A: 132 B: 176	47 (35–75); >60 in 6%	NR	Both: 30 mg bid postop until discharge A: 30 mg 1 h preop B: 40 mg qd x 10 d postdischarge		6 (4.5%) vs 0, *P*=.006, 4/6 after discharge; Risk higher for BMI >60 kg/m²: RR, 3 [30 d]	7 (5.3%) vs 1 (0.56%), *P*=.02 [30 d]
Brasileiro et al,[101] 2008 Prospective Single-institution	Bariatric surgery: 55% laparoscopic; BMI ≥40 or 35 to <40 kg/m² with comorbidities	126	43 (35–61) ≥40 in 72%	NR	40 mg preop + 40 mg/d x 15 d postop		1 (0.79%) symptomatic DVT; 0 asymptomatic [5 wk]	5[e] (3.9%), 1 (0.79%) fatal [50 wk]

(continued)

Appendix 2: Enoxaparin for VTE Prophylaxis in Obese Patients (cont.)

Study Design	Setting/ Inclusion Criteria	Obese, N	BMI,[a] kg/m^2	Weight,[a] kg	Dose and Regimen[b]	Anti-FXa [dose #][c]	VTE, n (%) [follow-up]	Major Bleeds, n (%) [follow-up]
Khoursheed et al,[102] 2013 Prospective Single-institution	Bariatric surgery: laparoscopic	39	45 (32–56)	122 (84–171)	40 mg qd preop + qd x 5 d postop	Met target [2,5][f]: 46%, 41% NS correlation with BMI/weight	1 (2.6%) fatal PE; 0/39 asymptomatic [6 wk]	NR
Celik et al,[76] 2015 Prospective Single-institution	Bariatric surgery: 92% laparoscopic; Weight A: <110 kg B: 110–150 kg C: >150 kg eGFR ≥30 mL/min	51 A: 17 B: 18 C: 18	42 (27–65) A: 37 B: 41 C: 49	128 (81–179) A: 100 B: 124 C: 171	40 mg q12h x 14 d postop	Below/met/above target [16–32][g,h]: A: 0%/65%/36% B: 0%/94%/6% C: 38%/63%/0% Correlated with weight and BMI (P<.001)	0 [mean, 12 d; range, 8-16]	0; 8 (16%) minor: A: 5 (29%) B: 2 (11%) C: 1 (5.6%) All had anti-FXa within target range [mean, 12 d; range, 8–16]
Escalante-Tattersfield et al,[103] 2008 Retrospective Single-institution	Bariatric surgery: laparoscopic; BMI ≥40 or >35 kg/m^2 with ≥2 comorbidities	618	49 (35–90)	137 (87–273)	UFH 5000 U preop + q8h x 24 h postop + enoxaparin, 40 mg q12h postop		1 (0.2%) asymptomatic DVT [52 wk]	10[i] (1.6%), all GI [52 wk]
Steele et al,[75] 2014 EFFORT Pilot double-blind, single-institution RCT (vs fondaparinux)	Bariatric surgery: laparoscopic BMI, 35–59 kg/m^2; C_{Cr} ≥30 mL/min	98	46	NR	40 mg bid postop	Met target [1][f]: 32%	2/83 (2.4%) asymptomatic DVT[j]; 0/98 symptomatic DVT [2 wk]	0; 4 (4.1%) minor [2 wk]
Wang et al,[66] 2014 Retrospective Multicenter	Hospitalized ≥48 h; Weight >100 kg; C_{Cr} ≥30 mL/min	9241 A: 6780 B: 2461	≥40 in 43%	Median, 116	A: 40 mg bid or UFH, 7500 U tid B: 40 mg qd or UFH, 5000 U bid/tid		BMI >40 kg/m^2: 35/2369 (1.48%) vs 12/1559 (0.77%), P=.05 BMI <40 kg/m^2: NS	BMI >40: NS BMI <40: NS[k]
Weight-Based Dosing								
Rondina et al,[77] 2010 Prospective	Hospitalized, medically ill, at risk for VTE; C_{Cr} ≥30 mL/min	28	48 (36–85)	136 (100–210); >120 in 75%	0.5 mg/kg qd x 2 d + as needed postop (mean, 67 mg [range, 50–105])	NS correlation with BMI/weight[l]	0 symptomatic [mean, 3 d]	0 [mean, 3 d]
Ludwig et al,[78] 2011 Retrospective Single-institution	Surgical ICU; C_{Cr} ≥30 mL/min	23	46 (36–77)	137 (97–267)	0.5 mg/kg bid x ≈18 doses (mean bid: 60 mg [range, 50–120])	Met target [3/4][l]: 91%	1 (4.3%) DVT (70 mg, likely preexisting) [mean, 46 d; range, 34–60]	0; 1 (4.3%) minor [mean, 46 d; range, 34–60]

(continued)

Appendix 2: Enoxaparin for VTE Prophylaxis in Obese Patients (cont.)

Study Design	Setting/ Inclusion Criteria	Obese, N	BMI,[a] kg/m^2	Weight,[a] kg	Dose and Regimen[b]	Anti-FXa [dose #][c]	VTE, n (%) [follow-up]	Major Bleeds, n (%) [follow-up]
Freeman et al,[79] 2012 Prospective	Hospitalized, medically ill; ≥1 VTE risk factor; BMI ≥40 kg/m^2; C_{cr} ≥30 mL/min	31 A: 11 B: 9 C: 11	62 (41–83)	176 (115–256)	A: 40 mg qd B: 0.4 mg/kg qd (mean, 70 mg/d [range, 50–90]) C: 0.5 mg/kg qd (mean, 92 mg/d [range, 80–130])	A, B, C Below target[h,i]: 82%, 36%, 13% (*P*<.001) Above target: 0, 1 (11%), 0 B, C: Met target [2]: 25%, 100% (*P*<.05) Not correlated with weight/BMI/C_{cr}	0 symptomatic [median, 3 d; 95% CI, 1–23]	0 [median, 3 d; 95% CI, 1–23]
Bickford et al,[64] 2013 Prospective Single-center	Trauma; BMI ≥30 kg/m^2; C_{cr} ≥30 mL/min	86	Median, 35 (IQR 10)	Median, 113 (IQR 30)	0.5 mg/kg q12h	Below/met/above target [3][f]: 5/86/9% No correlation with weight/BMI	16 (19%) vs 2 (2.3%) for before vs after enoxaparin, all DVT [≥7 d]	0 [≥7 d]
BMI-Based Dosing								
Borkgren-Okonek et al,[81] 2008 Prospective Open-label Single-institution	Bariatric surgery: 93% laparoscopic; A: BMI ≤50 kg/m^2 B: BMI >50 kg/m^2 Creatinine ≤1.6 mg/dL	208 A: 124 B: 99	A: 45 (36–50) B: 57 (51–82)	A: 126 (87–175) B: 161 (116–249)	UFH 5000 U preop + enoxaparin: A: 40 mg B: 60 mg q12h postop + qd x 10 d postdischarge	Below/met/above target [3]: A: 21%/79%/0% B: 14%/69%/17% 18/8% required dose increase/ decrease	1 (0.45%) overall: 1 (0.8%) vs 0 [mean, 77 ± 23 d]	5 (2.2%) total: 4 (3.2%) vs 1 (1%); 3 minor [mean, 77 ± 23 d]
Singh et al,[80] 2012 Retrospective Single-institution	Bariatric surgery: laparoscopic and open; BMI, kg/m^2 A: <40 B: 41–49 C: 50–59 D: >59	170 A: 11 B: 145 C: 9 D: 5	48 A: 39 B: 48 C: 51 D: 65	A: 108 B: 134 C: 149 D: 169	A: 30 mg B: 40 mg C: 50 mg D: 60 mg preop + bid postop		0 [>2 y]	5 (2.9%) A: 0 B: 4 (2.8%) C: 0 D: 1 (20%) [>2 y]

Abbreviations: BMI, body mass index; C_{cr}, creatinine clearance rate; DVT, deep venous thrombosis; eGFR, estimated glomerular filtration rate; FXa, factor Xa; GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range; NR, not reported; NS, not/no significant; PE, pulmonary embolism; postop, postoperative; preop, preoperative; PROBE, PRophylaxis against VTE Outcomes in Bariatric surgery patients receiving Enoxaparin; RR, risk ratio; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a]Mean (range), unless otherwise indicated.
[b]Dosing continued until discharge unless otherwise indicated.
[c]Anti-FXa levels measured at the peak, ≈4 h post-dose, with target range 0.18–0.44 U/mL, unless otherwise indicated. [dose #] is the dose after which the level was measured (ie, peak anti-FXa measured after the second dose would be annotated as [2]).
[d]All VTE occurred after discharge; 6 of 7 occurred off prophylaxis.
[e]Severity of 4 nonfatal postsurgery hemorrhages was not reported; 2 were due to spleen injury, 2 to staple-line bleeding.
[f]Anti-FXa target range for this study was 0.2–0.6 U/mL.
[g]Peak anti-FXa measured 3–5 h post-dose.
[h]Anti-FXa target range for this study: 0.2–0.5 U/mL.
[i]Bleeds were not clinically significant and did not require interruption or discontinuation of anticoagulation.
[j]No baseline imaging was performed, so DVT could have been preexisting.
[k]Severity of bleeds was not reported.
[l]Peak anti-FXa level measured 4–6 h post-dose.

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Appendix 3: Unfractionated Heparin for VTE Prophylaxis in Obese Patients

Study Design	Setting/ Inclusion Criteria	Obese, N	BMI[a], kg/m^2	Weight[a], kg	Dose and Regimen[b]	Anti-FXa [dose #][c]	VTE, n (%) [follow-up]	Major Bleeds, n (%) [follow-up]
Schauer et al,[104] 2000 Prospective Single-institution	Bariatric surgery: 99% laparoscopic	275	48 (35–68); >50 in 39%	NR	5000 U bid postop		2 (0.7%) PE; 1 (0.3%) DVT [mean, 9.4 mo; range, 1–31]	9 (3.3%) [mean, 9.4 mo; range, 1–31]
Higa et al,[105] 2001 Prospective Single-institution	Bariatric surgery: 99% laparoscopic	1500	(35–78)	NR	5000 U bid[d] postop		3 (0.2%) DVT; 3 (0.2%) PE [3 y]	12 (0.8%) [3 y]
Shepherd et al,[84] 2003 Prospective Single-institution	Medical and surgical hospitalized patients	245	Median, 28 (14–71); >35 in 25%	Median, 79 (34–193)	Adjusted to anti-FXa target[c] (median, 8000 U [3000–19,000]) q12h	Dose needed to meet target: (71.34 x weight) + (83.75 x height) – 3467.59		
	Bariatric surgery: 96% laparoscopic	700	NR	NR	Initial dose per equation above q12h postop		3 (0.4%), all PE, all nonfatal	16 (2.3%) with UFH stopped, 7 (1%) with transfusion; 4 (0.6%) minor
Miller & Rovito,[85] 2004 Retrospective Single-institution	Bariatric surgery: 98% laparoscopic; BMI, kg/m^2 A: <50 B: >50	255	50	138	A: 5000 U B: 7500 U preop + q8h postop		3 (1.2%), all off-drug, all symptomatic PE, 1 also had DVT [30 d]	6 (2.4%) [3 wk]
Prystowsky et al,[106] 2005 Prospective Single-institution	Bariatric surgery: 75% laparoscopic; BMI >60 kg/m^2	106	51 (40–73)	NR	5000 U preop + q12h postop		1/100 (1%) with no VTE history, 2/6 (33%) with previous VTE and IVC filter, all DVT [30 d]	2 (1.9%) [30 d]
McCullough et al,[107] 2006 Prospective Single-institution	Bariatric surgery; BMI >40 or >35 kg/m^2 with diabetes	109	49 (36–90)	NR	5000 U q12h postop		1 (2.7%) DVT; 1 (2.7%) PE [30 d]	4 (10.8%) [30 d]
Kothari et al,[100] 2007 Prospective Single-institution (vs enoxaparin)	Bariatric surgery: laparoscopic	238	47	135	5000 U preop + tid postop		1 (0.4%) PE [30 d]	3 (1.3%) [30 d]
Vaziri et al,[108] 2009 Prospective Single-institution	Bariatric surgery: 86% laparoscopic; ALL with IVC filters due to VTE history	29	49	NR	5000 U preop + q8h postop		6 (21%), all DVT, 4 at filter insertion site [mean, 16 ± 18 d]	NR

Abbreviations: BMI, body mass index; DVT, deep venous thrombosis; FXa, factor Xa; ISTH, International Society on Thrombosis and Haemostasis; NR, not reported; PE, pulmonary embolism; postop, postoperative; preop, preoperative; UFH, unfractionated heparin; VTE, venous thromboembolism; WMI, weighted mean incidence.

[a]Mean (range), unless otherwise indicated.

[b]Dosing continued until discharge unless otherwise indicated. All UFH doses were administered subcutaneously.

[c]Anti-FXa levels measured at the peak, ≈4 h post-dose, with target range 0.11–0.25 U/mL, unless otherwise indicated. [dose #] is the dose after which the level was measured (ie, peak anti-FXa measured after the second dose would be annotated as [2]).

[d]Per Becattini et al[82]; UFH dosing regimen is not indicated in primary report.

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Appendix 4: Fondaparinux for VTE Prophylaxis in Obese Patients

Study Design	Setting/ Inclusion Criteria	Obese, N	BMI[a], kg/m^2	Weight[a], kg	Dose and Regimen[b]	Anti-FXa [dose #][c]	VTE, n (%) [follow-up]	Major Bleeds, n (%) [follow-up]
Turpie et al,[86] 2002 Subgroup of meta-analysis of multicenter RCTs (vs enoxaparin)	Orthopedic surgery; BMI ≥30 kg/m^2; Creatinine ≤180 µmol/L	1296 A: 907 B: 970	NR	NR	A: 2.5 mg qd postop B: enoxaparin 30 mg bid or 40 mg qd postop		Significantly lower with fondaparinux [day 11]	NS between treatments [35–49 d]
Agnelli et al,[61] 2005 Subgroup of double-blind double-dummy RCT (vs dalteparin)	Abdominal surgery >45 min; Age >60 y or >40 y with ≥1 VTE risk factor; BMI >30/>28.6 kg/m^2 for men/women; Creatinine ≤180 µmol/L	315	NR	NR	2.5 mg qd x 5–9 d postop		BMI is a risk factor; OR, 1.08 (95% CI, 1.04–1.12) per kg/m^2 [30 ± 2 d]	Not correlated with BMI or C_{Cr} [30 ± 2 d]
Martinez et al,[87] 2011 Retrospective Single-institution	Hospitalized; BMI ≥40 kg/m^2; C_{Cr} ≥30 mL/min (range 42-349)	45	51 (40–99)	142 (96–300)	2.5 mg qd	Below/met/above target: 47%/43%/11% Anti-FXa negatively correlated with BMI (P=.009), C_{Cr}	0 [30 d]	1 (2.2%); 1 (2.2%) minor; Both had anti-FXa within target range [30 d]
Steele et al,[75] 2014 EFFORT Pilot double-blind single-institution RCT (vs enoxaparin)	Bariatric surgery: laparoscopic; BMI, 35–59 kg/m^2; C_{Cr} ≥30 mL/min	100	45	NR	5 mg qd postop	Met target [1][d]: 74%	2/92 (2.2%) asymptomatic DVT[e]; 0/100 symptomatic DVT [2 wk]	0; 4 (4.0%) minor [2 wk]

Abbreviations: BMI, body mass index; C_{Cr}, creatinine clearance rate; DVT, deep venous thrombosis; FXa, factor Xa; NR, not reported; NS, not/no significant; OR, odds ratio; postop, postoperative; preop, preoperative; RCT, randomized controlled trial; VTE, venous thromboembolism.

[a]Mean (range), unless otherwise indicated.

[b]Dosing continued until discharge unless otherwise indicated.

[c]Anti-FXa levels measured at the peak, ≈4 h post-dose, with target range 0.3–0.5 mg/L, unless otherwise indicated. [dose #] is the dose after which the level was measured (ie, peak anti-FXa measured after the second dose would be annotated as [2]).

[d]Anti-FXa target range for this study was 0.39–0.50 mg/L.

[e]No baseline imaging was performed, so DVT could have been preexisting.

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