Published in final edited form as:
Expert Rev Cardiovasc Ther. 2010 December ; 8(12): 1711–1721. doi:10.1586/erc.10.160.

Prevention of venous thromboembolism in obesity

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Abstract

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in hospitalized patients. Where appropriate, evidence-based methods of prophylaxis are implemented and the burden of VTE can be reduced substantially. Obesity, including morbid obesity, is associated with a high risk of VTE and, unfortunately, fixed doses of US FDA-approved anticoagulant regimens, including unfractionated heparins, low-molecular-weight heparins and factor Xa inhibitors, may not provide optimal VTE prophylaxis in these patients. Although the data are still limited, a rapidly growing body of literature and cumulative evidence suggests that anticoagulant dose adjustments in morbidly obese patients may optimize pharmacodynamic activity and reduce VTE risk. With the prevalence of morbid obesity continuing to rise, more high-quality clinical data are needed to better understand the pathobiology of VTE in obesity and provide effective, yet safe, prevention strategies.

Keywords

deep vein thrombosis; fondaparinux; low-molecular-weight heparin; morbid obesity; pulmonary embolism; special populations; venous thromboembolism prophylaxis

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality, occurring in up to 1 million people and accounting for over 200,000 deaths annually in the USA [1,101]. Importantly, more than half of VTE cases are attributable to the hospital or surgical setting [2]. Furthermore, autopsy studies demonstrate that 10–15% of hospital deaths can be attributed to fatal PE, which has been cited as the most common preventable cause of hospital death [1,3–5]. Chemical thromboprohylaxis (e.g., heparin, low-molecular-weight heparin [LMWH] and fondaparinux) has been shown to substantially reduce this risk of VTE in both medical and surgical populations [4,6–9], and in September 2008 the Surgeon General issued a “call to action to prevent deep vein thrombosis and pulmonary embolism,” emphasizing the importance of VTE prevention [101].

Obesity has been demonstrated to be an independent risk factor for VTE in both men and women [10–13]. Updated data from the 2008 National Health and Nutrition Examination

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Survey (NHANES) estimates that 33.8% of US adults are obese (BMI ≥30 kg/m^2) and 5.7% are morbidly obese (BMI ≥40 kg/m^2) [14]. Unfortunately, our understanding of how to provide adequate VTE thromboprophylaxis to this growing segment of the population is limited as, outside of bariatric surgery groups, severely obese patients have been consistently under-represented in studies of thromboprophylaxis. This article reviews the current information on the risk of VTE attributable to obesity, proposed underlying pathophysiologic mechanisms, pharmacologic and mechanical methods for thromboprophylaxis in obese patients and, when feasible, provides practical recommendations for prophylaxis in this special patient population.

Patients with obesity have an enhanced risk of VTE

Obesity was suspected as a risk factor for VTE as early as the 1920s in patients who suffered fatal postoperative PE, but consensus for obesity as an independent risk factor in both men and women has only recently developed [11,12,15,16]. In 2005, Stein and colleagues showed a relative risk (RR) in obese patients over twice that of nonobese patients for both PE (RR: 2.18; 95% CI: 2.16–2.19) and DVT (RR: 2.50; 95% CI: 2.49–2.51), and an incredible fivefold risk in patients under the age of 40 years (RR of PE: 5.19; CI: 5.11–5.28; RR of DVT: 5.2; 95% CI: 5.15–5.25) [11]. Recent data from the Nurses' Health Study illustrate that an increasing BMI has a strong linear association with the development of PE in women, with a nearly sixfold risk increase in subjects with a BMI of 35 kg/m^2 or more [17].

Obesity also adds substantially to other known risk factors for developing VTE. In 2010, a VTE subcohort from the Danish prospective Diet, Cancer and Health study was examined for the combined risk of obesity and genetic mutations F5 G1691A (Factor V Leiden) and F2 G20210A (prothrombin) on the risk of first VTE. Obesity doubled the hazard ratio (HR) for developing VTE in patients with Factor V Leiden (HR: 5.27; 95% CI: 2.74–10.14 vs 2.63; 95% CI: 1.62–4.28) and more than quadrupled the risk in patients with prothrombin mutation (HR: 6.89; 95% CI: 1.18–40.22 vs 1.43; 95% CI: 0.44–4.63) [18]. Similarly, the combination of oral contraceptive (OCP) use and obesity has been shown to increase the odds ratio of DVT from 5.2 to 7.8 compared with obese women not taking OCPs and by 3.1 over nonobese users of OCPs [19]. Finally, obese patients have a substantially greater risk of recurrent VTE compared with normal-weight controls. Eichinger *et al.* demonstrated that among 1107 patients after a first unprovoked VTE and cessation of anticoagulation, the probability of recurrent PE was 9.3% among normal-weight patients, 16.7% among overweight patients (BMI 25–29 kg/m^2) and 17.5% among obese patients (BMI ≥30kg/m^2) [20].

Obesity is regarded as a prothrombotic state and several derangements of normal hemostasis are thought to contribute to the process (Box 1). In animal studies of obesity, the overproduction of adipokines such as leptin and adiponectin, insulin resistance and a chronic low-grade inflammatory state have been linked with enhanced platelet reactivity [21]. Leptin has also been demonstrated *in vitro* to trigger coagulation by upregulation of tissue factor expression in peripheral blood mononuclear cells and circulating procoagulant tissue factor has been identified in circulating monocytes and microparticles at increased levels in morbidly obese patients [22–24]. Thrombin generation, a marker of the overall coagulation potential, is increased in patients with morbid obesity, is reduced following weight loss after bariatric surgery, and is paralleled by known cardiovascular risk reduction [25]. Another significant mechanism is the inhibition of fibrinolysis by the overproduction of plasminogen activator inhibitor-1 from adipocytes and hepatocytes driven by increased circulating free fatty acids, proinflammatory cytokines, adipokines and even relative hypoxia in adipose tissue in obesity [26].

Finally, venous stasis is common in obesity and promotes endothelial activation, predisposing patients to thrombosis [27]. Low flow in stasis may also allow for the accumulation of prothrombotic substances, such as thrombin, in large vessels rather than being washed downstream where they are inactivated. This favors the hypoxic activation of endothelial cells in the vessel wall and diminishes the ability of the metalloprotease ADAMS13 to cleave hyperadhesive ultra-large multimers of von Willebrand factor [27].

Box 1. Proposed thrombotic mechanisms in obesity

Enhanced platelet activity

- Adipokinins (leptin, adiponectin)
- Insulin resistance
- Low-grade inflammation
- Stasis resulting in UL-vWF

Procoagulant state

- Increased tissue factor
- Increased fibrinogen, factor VII and factor VIII
- Increased thrombin generation

Impaired fibrinolysis

- Overproduction of PAI-1 and TAFI

Activation of endothelial cells

- Tissue hypoxia

PAI-1: Plasminogen activator inhibitor-1; TAFI: Thrombin-activatable fibrinolysis inhibitor; UL-vWF: Ultra-large von Willebrand factor.

VTE prevention with pharmacologic agents

Chemical thromboprophylaxis using unfractionated heparin (UFH), LMWHs and the available factor (F)Xa inhibitor fondaparinux reduces the RR of VTE by 45–63% in admitted medical patients and by at least 60% in general surgery patients compared with no prophylaxis [4,6,7,9]. While pharmacologic dosing of these agents has been well characterized for normal-weight patients, dosing in obese patients presents several challenges owing to changes in both drug distribution and pharmacokinetics. Obese patients have an increased percent of fat per kilogram of total body weight (TBW), resulting in an increased volume of distribution of lipophilic drugs. However, the relative reduced vascularity of adipose tissue may result in overdosing of medications with large vascular distribution when dosing by TBW [28,29].

The 2008 American College of Chest Physicians (ACCP) guidelines on the prevention of VTE recommend the use of either UFH, LMWH or fondaparinux for thromboprophylaxis in moderate- and high-risk general surgery, bariatric surgery and medical patients with risk factors for VTE, such as active cancer, previous VTE, ischemic stroke and inflammatory bowel disease [4]. However, in most pharmacodynamic and clinical studies of thromboprophylaxis using these agents, obese (BMI ≥30 kg/m^2) and morbidly obese (BMI ≥40 kg/m^2) patients have been under-represented. Although the data are limited, below we summarize the available information on dosing of UFH, LMWH and fondaparinux in obese and morbidly obese patients.

Low-dose UFH

The 2008 ACCP guidelines recommend low-dose UFH as one of several options for prophylaxis in medical patients with VTE risk factors, general surgery and bariatric surgery patients, and specifically recommend UFH dosed thrice-daily for bariatric surgery and high-VTE-risk surgical patients. However, few studies utilizing UFH for thromboprophylaxis have specifically examined patients at the extremes of body weight for pharmacodynamic or clinical outcomes (TABLES 1 & 2). In healthy-weight patients, low-dose (e.g., 5000 units [U] every 12 h), subcutaneous (s.c.) UFH has poor plasma recovery [30] and inconsistent pharmacokinetics. Additionally, the s.c. absorption of heparin can be affected by the amount of adipose tissue, a point exacerbated in obesity [31].

In a series of 700 obese (BMI >35 kg/m^2) patients undergoing laparoscopic Roux-en-Y using an adjusted-dose, heparin anti-FXa-monitored protocol for s.c. UFH, VTE occurred as nonfatal PE in 0.4% of patients and bleeding requiring transfusion in 1% [31]. This protocol was developed based on a mixed series of medical and surgical patients (median BMI: 28 kg/m^2; range: 14–71 kg/m^2) where the median 12 h s.c. UFH dose required to achieve the goal anti-FXa activity (0.11–0.25 U/ml) was 8000 U (range: 3000–19,000 U) [31]. Other investigators have examined low-dose continuous intravenous (i.v.) UFH infusions as an alternative method of prophylaxis in bariatric surgery [32,33]. In one series of 822 patients (mean BMI: 45 kg/m^2; range: 30–86), i.v. UFH at 400 U/h (9600 U/day) was assessed with dosing initiated preoperatively and was continued until hospital discharge. Clinically evident VTE occurred in 0.12% of patients and major bleeding in 1.3% [33].

These studies suggest that larger than standard doses of UFH may be warranted to provide optimal VTE prophylaxis in morbidly obese patients, but the scarcity of adequately designed and controlled trials limits more specific dosing recommendations.

Low-molecular-weight heparins

Because of the unpredictable bioavailability and anticoagulant effects of UFH, LMWHs are being increasingly used in place of UFH. Following s.c. administration, LMWHs accumulate predominantly in blood and vascular tissue with a bioavailability approaching 100% even at low doses [30]. Importantly, LMWHs have considerable renal clearance and so doses may be reduced in patients with a creatinine clearance of less than 30 ml/min [30]. Since intravascular volume does not have a linear relationship with TBW, there have been some concerns that LMWHs could be overdosed if administered based upon TBW in obese patients. Conversely, obese patients appear to be at higher risk of VTE than non-obese patients – even when standard fixed-dose LMWH prophylaxis is used – and the potential for underdosing using standard prophylactic doses remains high [34].

Anti-FXa monitoring using LMWH

Laboratory monitoring of the anticoagulant activity of LMWH is not required in the majority of patients [30]. However, because the original trials examining the efficacy and safety of LMWH included highly selected patients, the American College of Pathology and ACCP Guidelines recommend that laboratory monitoring be considered in select patients receiving LMWH, including those who are overweight [30,35]. Although the debate over the utility of laboratory testing with LMWH dosing is ongoing, monitoring in special patient groups, including the obese, remains recommended [36,37]. The most consistent and widely used laboratory test for LMWH has been the anti-FXa activity assay and for therapeutic dosing with twice-daily LMWH, the recommended range for peak anti-FXa activity assessed 4 h after dosing is 0.6–1.0 U/ml. For prophylactic dosing, the optimal peak anti-FXa level is unknown since monitoring of prophylactic-dose LMWH is generally not

performed. However, peak anti-FXa levels of 0.2–0.5 IU have been suggested by some authors [36,38].

Pharmacodynamic data using LMWH

In pharmacodynamic studies of therapeutic LMWH dosing in obese patients (maximum weight 190 kg), dosing by TBW, without capping the dose, leads to acceptable therapeutic peak anti-FXa levels, and noninferior or improved clinical efficacy over therapeutic UFH without increased bleeding (TABLE 1) [39–42]. Similarly, pharmacodynamic studies of VTE prophylaxis using LMWHs also suggest that higher than standard or weight-adjusted dosing is superior at achieving target anti-FXa levels. For example, prophylactic dosing with enoxaparin in healthy volunteers or hospitalized medical patients at a standard fixed dose of 40 mg daily (the US FDA-approved dose in medically ill patients) and peak anti-FXa levels in patients with a BMI more than 26 kg/m^2 correlate in a negative fashion with increasing body weight [43,44] and are often below recommended (i.e., <0.2 U/ml) target anti-FXa levels for VTE prevention [45]. Conversely, weight-based prophylactic dosing of tinzaparin at 75 IU/kg in healthy volunteers led to consistently appropriate (i.e., >0.2 U/ml) anti-FXa levels regardless of weight without any evidence of excessive dosing at higher weights [46]. Although encouraging, these data in healthy volunteers are not easily extrapolated to acutely ill, hospitalized medical patients. Using a weight-based prophylactic dosing regimen of enoxaparin (0.5 mg/kg s.c. once daily using TBW, with no dose 'cap') in hospitalized obese medical patients (average BMI: 48.1 kg/m^2; SD: ±11.1) weighing up to 210 kg, target anti-FXa levels (0.2–0.5 U/ml) for VTE prophylaxis with LMWHs were achieved in most patients (average peak anti-FXa: 0.25; SD ±0.11), regardless of weight or BMI [47]. Importantly, no patients had a peak anti-FXa level within the therapeutic range (i.e., >0.6 U/ml). These data suggest that in morbidly obese medical patients, weight-based dosing of LMWHs for VTE prophylaxis leads to consistent and appropriate peak anti-FXa levels.

Studies in bariatric surgery patients have also demonstrated that higher enoxaparin dosing leads to a higher proportion of the anti-FXa levels in a recommended range for thromboprophylaxis. When 30 mg enoxaparin given s.c. every 12 h was compared with 40 mg every 12 h in 52 bariatric surgery patients, the average peak anti-FXa levels after the third dose were 0.08 and 0.15 U/ml, respectively ($p < 0.05$). Even in the 40-mg group, however, appropriate levels (defined by the authors as 0.18–0.44 U/ml) were only reached in 41.7% of patients [48]. In a similar study of 40 versus 60 mg of enoxaparin given every 12 h, average anti-FXa levels were higher in the 60-mg group (0.43 vs 0.21 U/ml; $p < 0.001$). Patients receiving 60 mg every 12 h were less likely to have subprophylactic (defined as <0.18 U/ml) anti-Xa levels (0 vs 44%), but anti-FXa levels above the prophylactic range (defined as >0.44 U/ml) were more frequent in this group (57 vs 0%), though no bleeding events occurred [49]. Additionally, Imberti *et al.* demonstrated that increasing the prophylactic dosing of the LMWH parnaparin from a fixed dose of 4250 IU/day to a fixed dose of 6400 IU/day in bariatric surgery patients (BMI range: 36.1–64.1 kg/m^2) resulted in supraprophylactic anti-FXa levels (defined as >0.4 U/ml) in 62.3% of patients. By contrast, only approximately 2% of patients who received the lower dose developed a supratherapeutic (>0.4 U/ml) anti-FXa level [29].

Although these data support the recommendations in the ACCP guidelines that higher than usual doses should be considered in obese patients [4], the TBW in many of the studies was highly variable and there is continued uncertainty as to whether LMWH dosing in bariatric surgery patients should be based on BMI or TBW (as adiposity has a different vascular composition than lean body mass). Until there are more definitive data, specific recommendations on the optimal dose of LMWHs in bariatric surgery patients, beyond those made in the ACCP guidelines, remain elusive. For medical patients, there is evolving

evidence to support weight-adjusted LMWH dosing using TBW, which may lead to predictable target anti-FXa levels.

Clinical data using LMWH

Though pharmacodynamic studies have demonstrated the effectiveness of weight-based dosing for some LMWHs (TABLE 2), no prospective, randomized, appropriately controlled clinical trials have been published. Yet, observational data sets do suggest that in morbidly obese admitted medical or surgical patients receiving FDA-approved fixed doses of LMWHs, VTE rates may be unacceptably high. For example, in a retrospective analysis of 817 patients undergoing orthopedic surgery using a standard fixed dose of enoxaparin at 40 mg per day, the incidence of VTE in obese patients was nearly double that of nonobese patients (31.8 vs 16.7%; $p < 0.001$) [34]. Similarly, in a subgroup analysis of 1118 obese patients from the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial, in which admitted medical patients received a fixed dose of dalteparin 5000 IU/day, dalteparin had no benefit over placebo in patients with a BMI of 40 kg/m^2 or more (3.3% of all patients), suggesting a standard fixed dose of dalteparin is insufficient at more extreme body weights [50].

In comparison, higher doses of LMWHs may lower the risk of VTE compared with standard FDA-approved fixed doses. In a prospective, nonrandomized study of bariatric surgery patients given either enoxaparin 30 or 40 mg s.c. every 12 h, postoperative VTE was lower with the higher dosing regimen (0.6 vs 5.4%; $p < 0.05$) without a significant difference in bleeding complications. However, patients in the lower-dose group did have longer operative times and hospital stays, highlighting the nonrandomized nature of this study and introducing the potential for bias [51]. Similarly, Borkgren-Onkonek *et al.* demonstrated that using a BMI-stratified dosing regimen for enoxaparin (40 mg every 12 h for BMI <50 kg/m^2 or 60 mg every 12 h for BMI >50 kg/m^2 during hospitalization, then daily for 10 days) in 223 Roux-en-Y gastric bypass patients, target anti-FXa levels were achievable, bleeding rates were low (1.79%) and VTE occurred in only one patient (0.45%) [52].

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that works by potentiating FXa inhibition through binding to antithrombin. Similar to the LMWHs, this agent is nearly 100% bioavailable by s.c. administration and is predominantly cleared by the kidneys, but has a longer half-life than LMWH (~16 vs 4–6 h). A meta-analysis of four randomized controlled trials comparing fondaparinux with enoxaparin in major orthopedic surgery demonstrated a greater than 50% risk reduction of total VTE at hospital day 11 in patients receiving 2.5 mg of fondaparinux daily without an increase in major bleeding. For the four included studies, the average BMI ranged from 24 to 31 kg/m^2, average weight ranged from 64 to 89 kg with a maximum of 223 kg, and percent of obese patients ranged from 5.4 to 53% of the total patients. Although all the studies used a fixed dosing regimen (fondaparinux 2.5 mg daily vs either 30 mg twice daily or 40 mg daily enoxaparin), this risk reduction remained significant in obese patients (odds reduction of 54%) [53]. Similarly, in a subgroup analysis of over 600 obese patients undergoing high-risk abdominal surgery (maximum weight 215 kg), there was no significant difference in the incidence of postoperative VTE at day 10 or bleeding rates using 2.5 mg of daily fondaparinux versus 5000 IU of dalteparin daily [54]. Though laboratory monitoring is not routinely performed for fondaparinux, recent data on the pharmacodynamic parameters in ten morbidly obese healthy volunteers (mean BMI 51.5 kg/m^2; maximum BMI 76.6 kg/m^2) up to 248 kg demonstrated that 5-mg fondaparinux achieved a target level, while the 2.5-mg dose did not [55].

Based on subgroup analyses from published studies, current FDA-approved doses of fondaparinux appear to be effective in obese patients (TABLES 1 & 2). In addition, emerging pharmacokinetic data suggest that in extreme-weight patients, higher doses achieve target anti-FXa levels. Though these data are intriguing, as fondaparinux does not have a clearly established reversal agent, higher doses may increase the risk of bleeding and warrant more study before being recommended for routine use. Until these data are available, fondaparinux should be used at currently approved doses.

VTE prevention with nonpharmacologic strategies

Nonpharmacologic strategies for VTE prevention have traditionally included mechanical devices such as graduated compression stockings, venous foot pumps and intermittent pneumatic compression devices. These mechanical methods (MDs) have the advantage of reducing VTE risk without increasing bleeding risk, but limitations exist. Although MDs have been employed adjunctive to pharmacologic prophylaxis (i.e., 'multimodality prophylaxis') in bariatric surgery and medically ill morbidly obese patients [49,56], they have not been studied sufficiently in large, randomized, adequately powered and designed trials as monotherapy in patients with morbid obesity. In addition, MDs may be less effective than pharmacologic prophylaxis [57], are associated with relatively poor compliance in real-world settings, and consequently are recommended for use only as an adjunct to chemical prophylaxis or as monotherapy in patients with a high risk of bleeding [4]. As a result, consistent with the ACCP guidelines, the use of MDs alone (without pharmacologic prophylaxis) for VTE prevention in patients with morbid obesity cannot be recommended unless a high bleeding risk precludes the use of pharmacologic prophylaxis [4].

Because patients undergoing bariatric surgery may have a high risk of VTE postoperatively and many of these complications occur despite pharmacologic prophylaxis [56,58], inferior vena cava filters (IVCFs) are being used with increasing frequency. For example, a recent survey found that the use of IVCFs as VTE prophylaxis during bariatric surgery has increased approximately eightfold during a 10-year period [59,60].

A systematic review of 11 published studies of IVCF use in higher risk, bariatric surgery patients was recently published [61]. In aggregate, these data do suggest that retrievable IVCF placement in bariatric surgery patients results in a low rate of complications and may reduce postoperative PE, particularly in high-risk bariatric surgery patients. Although intriguing, several limitations, as highlighted by these authors, may temper initial enthusiasm. None of the 11 studies included in the systematic review was a randomized trial and eight were case series. The definition of 'high risk' varied among studies, although some features included a BMI over 50 kg/m^2, history of VTE and venous insufficiency. Pharmacologic and mechanical methods of VTE prophylaxis in these trials differed substantially and, arguably, may not always have been optimal. Only four of the studies compared IVCF to no IVCF and two of these four cohort studies were unable to demonstrate a significant difference in PE between the two groups. Finally, complications of IVCF placement (including insertionsite thrombosis, DVT, post-thrombotic syndrome and filter migration) may not have been adequately considered. Given the limitations of these and other data, and the potential short- and long-term complications of IVCFs, until data from high-quality, randomized clinical trials have been published, the routine use of retrievable IVCF placement in bariatric surgery patients is not supported by the available evidence [61,62].

Expert commentary

Venous thromboembolism, including fatal PE, is a catastrophic medical condition that for most is intimately linked to transient heightened periods of risk such as hospitalization and surgery. The routine implementation of effective thromboprophylaxis in these at-risk patients is effective, safe, cost effective and has the potential to save thousands of lives annually in the USA. Yet, effective VTE prevention, as it relates to chemical prophylaxis, implies using drugs at the appropriate dose, interval and duration. For many, appropriate dosing is explicit and is based upon results of high-quality randomized clinical trials. Obese patients are an important at-risk group owing to the increasing prevalence of obesity in the USA, the increased contribution of obesity to VTE risk, and the relative under-representation of these patients in thromboprophylaxis clinical trials. There is increasing certainty that FDA-approved fixed-dose thromboprophylaxis regimens are not sufficient in obese patients, but optimal dosing of thromboprophylaxis in these patients remains uncertain. Current practice guidelines by the ACCP recommend that for patients undergoing inpatient bariatric surgery, higher doses of LMWH or low-dose UFH be used rather than the usual doses used for nonobese patients and suggest that the use of weight-based dosing of LMWH prophylaxis should be considered [63]. From a practical viewpoint, and one which is based upon the limited published data, clinicians can choose one of several options when approaching these patients:

- Subcutaneous UFH given thrice daily at a dose of at least 5000 U per dose (higher doses may be indicated, but available evidence does not allow for specific dosing recommendations). Alternatively, heparin doses can be adjusted to achieve 2–4 h postinjection heparin anti-FXa levels or activated partial thromboplastin time (APTT) in target range (in general, anti-FXa levels of approximately 0.1–0.4 IU/ml or APTT in the upper normal range). This latter strategy has been shown to be effective in orthopedic patients, but has not been assessed specifically in the obese [4];
- Low-molecular-weight heparin given either at increased fixed doses (e.g., enoxaparin 40 mg every 12 h or dalteparin 5000 IU every 12 h) or preferably weight-based doses using actual body weight (e.g., anti-FXa 40–75 IU/kg once daily) with or without accompanying peak anti-FXa-level monitoring. As stated, the current recommendations by the ACCP guidelines are to consider weight-based dosing [63];
- Fondaparinux 2.5–5 mg s.c. once daily; importantly, there are limited data for adjusting fondaparinux doses in relation to obesity and owing to the long elimination half-life of this drug, along with the lack of a reversal agent, more data are needed before dose adjustments can be recommended.

Until there are comparative clinical outcomes data, the decision of which strategy to use should be dependent on an individual patient's risk of both thrombosis and bleeding, clinician comfort and experience, availability of laboratory monitoring and cost. With the continued rise in obesity in the USA, future clinical trials involving thromboprophylaxis should be designed to ensure adequate representation of obese patients, and strong consideration given to implementing protocol-specified adjusted strategies in these patients.

Five-year view

Several new agents, including the oral direct thrombin inhibitors and FXa inhibitors – some of which are already approved outside the USA – will likely receive FDA approval for the prevention of VTE in the coming years. Although current and evolving evidence suggests that several of these agents may be effective and safe for many patient-related indications,

there is little published experience with these newer agents in patients with morbid obesity. As such, there will be an urgent need for good-quality data in patients with morbid obesity. Early subgroup analysis of large comparative clinical trials will provide the needed early insight into the relative efficacy and safety of these drugs in obese patients. Until these data are available, weight-based dosing algorithms and/or arbitrary dose increases in pharmacologic agents will likely be incorporated with increasing frequency into routine clinical use. In addition, we may see refinement of national guidelines and quality measures, incorporating dose adjustments for patients with morbid obesity.

From a mechanistic perspective, ongoing studies into the contribution of adipokines, such as leptin and adiponectin, will hopefully advance our understanding of the pathobiology of obesity and the risk of VTE and may lead to novel preventive approaches. During this time, efforts to reduce the burden of obesity through lifestyle modifications, pharmacologic agents, and patient and provider education will continue.

Acknowledgments

We would like to thank Kim Mahoney and Sharla Watts for their help and support in preparing this manuscript.

This work was supported by the NIH (grant no. 1K23HL092161 and R43 HD066993). Robert C Pendleton is on the speaker's bureau for Sanofi-Aventis and has received grant support from the NIH, ARUP Laboratories, Sanofi-Aventis, Boehringer Ingelheim, Pfizer, Canyon's Pharmaceuticals and Bristol-Meyers Squibb. Matthew T Rondina is on the speaker's bureau for Sanofi-Aventis and GSK and has received grant support from Sanofi-Aventis and Pfizer.

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Table 1

Pharmacodynamic studies on the use of low-molecular-weight heparin and fondaparinux for venous thromboembolism prophylaxis in obese patients.

Study, year (n)	Study design	Population	Obese (%)	Maximum weight (kg)	Agent and dose	Target anti-FXa prophylactic range (units/ml)	Peak (4-h) anti-FXa levels (units/ml)	Comments	Ref.
Frederiksen *et al.*, 2003 (19)	PC	Surgical	NR	~150	Enoxaparin 40 mg single dose	NR	NR	Negative correlation with increasing body weight	[43]
Hainer *et al.*, 2002 (37)	Prospective open label†	Healthy, heavyweight subjects (vs historical controls <100 kg)	97	165	Tinzaparin 75 IU/kg	NR	Nonobese: 0.30 (range: 0.28–0.32); obese: 0.34 (range: 0.303–0.375)	Predictable response maximum anti-FXa activity regardless of body weight	[46]
Simone *et al.*, 2008 (40)	PC	Bariatric surgery	100	NR	Enoxaparin 40 mg b.i.d. vs 60 mg b.i.d.	0.18–0.44	Nonobese: 0.21 vs obese: 0.43 ($p < 0.001$)	Subtherapeutic (<0.18 u/ml) 44 vs 0%; supratherapeutic (>0.44 u/ml) 0 vs 57%	[49]
Borkgren-Onkonek *et al.*, 2008 (223)	Prospective open label	Bariatric surgery	100	NR	Enoxaparin 40 mg b.i.d. if BMI <50 and 60 mg b.i.d. if BMI >50	0.18–0.44	Nonobese: 0.32 vs obese: 0.26	1 nonfatal VTE (0.45%) Major bleeding: 1.79%	[52]
Rowan *et al.*, 2008 (52)	PC	Bariatric surgery	100	NR	Enoxaparin 30 mg b.i.d. vs 40 mg b.i.d.	NR	Nonobese: 0.008 vs obese: 0.15 ($p < 0.05$) for third dose		[48]
Imberti *et al.*, 2009 (66)	Multicenter open label, pilot study of RCT	Bariatric surgery	100	Maximum BMI 64.1 kg/m^2	Parnaparin 4250 IU/day vs 6400 IU/day	0.1–0.4	Nonobese: 4150 U dose 98% in range; obese: 62.3% 6400 IU/day out of range	Anti-FXa level did not correlate with BMI when compared above and below BMI 45 (BMI range: 36.1–64.1)	[24]
Mayr *et al.*, 2002 (89)	PC	General and surgical ICU	NR	~150	Enoxaparin 40 mg/day	0.1–0.3		High body weight significantly correlated with low anti-Fxa	[44]
Jimenez *et al.*, 2008 (112)	PC	Medically ill, respiratory illness	21	NR	Enoxaparin 40 mg/day	0.2–0.6	BMI <23: 0.28; BMI 23–26: 0.23; BMI 26–29: 0.15; BMI >30: 0.13		[45]

Study, year (n)	Study design	Population	Obese (%)	Maximum weight (kg)	Agent and dose	Target anti-FXa prophylactic range (units/ml)	Peak (4-h) anti-FXa levels (units/ml)	Comments	Ref.
							($p < 0.002$)		
Rondina *et al.*, 2010 (28)	PC	Medically ill, respiratory illness	100	210	Enoxaparin 0.5 mg/kg once daily	0.2–0.6	0.25 u/ml (SD: 0.11)	Anti-FXa levels did not correlate with BMI using weight-based dosing	[47]
Raftopoulos *et al.*, 2008 (10)	Prospective randomized crossover study	Morbidly obese volunteers	100	248	Fondaparinux 2.5 mg daily vs 5 mg daily	Maximum concentration 0.34‡	2.5-mg dose: 0.21 (SD: 0.08); 5-mg dose: 0.41 (SD: 0.16)	Lower dose did not reach target levels for maximum concentration	[55]

†Cohort compared with normal historical controls.

‡Reported as maximum fondaparinux plasma concentration mean (range).

b.i.d.: Twice per day; FXa: Factor Xa; ICU: Intensive care unit; LMWH: Low-molecular-weight heparin; NR: Not reported; PC: Prospective cohort; RCT: Randomized controlled trial; SD: Standard deviation; VTE: Venous thromboembolism.

Data taken from [64].

Expert Rev Cardiovasc Ther. Author manuscript; available in PMC 2011 December 26.

Table 2

Clinical studies on the use of low-molecular-weight heparin, fondaparinux and unfractionated heparin for venous thromboembolism prophylaxis in obese patients.

Study, year (n)	Study design	Population	Obese (%)	Agent and dose	Mechanical prophylaxis	BMI (kg/m^2)	Outcomes			Ref.
							VTE/MB	*Nonobese*	*Obese*	
Kucher *et al.*, 2005 (3706)	RCT retrospective subgroup analysis	Medically ill	30	Dalteparin 5000 U/day	NR	Mean BMI >30 (men); BMI >28 (women)	VTE by day 21 (MB)	2.8% (95% CI: 1.6%)	2.8% (95% CI: 0%)	[50]
				Placebo				5.2% (95% CI: 0.3%)	4.3% (95% CI: 0.7%)	
Samama *et al.*, 1995 (817)	Retrospective analysis	Orthopedic surgery	NR	Enoxaparin 40 mg/day	NR	BMI >32	VTE	16.7%	31.8% ($p < 0.001$)	[37]
Scholten *et al.*, 2002 (481)	Prospective cohort	Bariatric surgery	100	Enoxaparin 30 mg every 12 h	EA, GCS, IPC	Mean BMI 50–51	VTE (MB)		5.4% (95% CI: 1.1%)	[51]
				40 mg every 12 h					0.6% (95% CI: 0.3%)	
Escalante-Tattersfield *et al.*, 2008 (618)	Retrospective analysis	Bariatric surgery	100	Enoxaparin 40 mg every 12 h	EA, IPC, high-risk IVCF	BMI >35	VTE (MB)		0.16% (95% CI: 1.6%)	[65]
Magee *et al.*, 2010 (735)	Retrospective cohort	Bariatric Surgery	100	Dalteparin 2500 IU preoperatively, 5000 IU daily post-operatively	EA, high-risk IVCF		Symptomatic VTE compared with HC		0 VTE events at 6 months–11 years, HC: 1.9–3.5% (MB: 0.4%)	[66]
Agnelli *et al.*, 2005 (2858)	RCT subgroup analysis	High-risk abdominal surgery	22	Fondaparinux 2.5 mg s.c.	NR	BMI >30 (men); BMI >28.6 (women)	VTE (MB)	4.6% (95% CI: 3.4%)	8.6% (2.9%)	[54]
				Dalteparin 5000 U/day				6.1% (95% CI: 2.4%); NS	6% (95% CI: 2.2%); NS	
Turpie *et al.*, 2002 (5252)	Subgroup analysis	Orthopedic surgery	25	Fondaparinux 2.5 mg s.c. q.d.	NR	BMI ≥30	VTE up to day 11		42/628 patients (7.6%)	[53]

Study, year (n)	Study design	Population	Obese (%)	Agent and dose	Mechanical prophylaxis	BMI (kg/m^2)	Outcomes			Ref.
							VTE/MB	*Nonobese*	*Obese*	
				Enoxaparin 30 mg b.i.d. or 40 mg q.d.					102/668 patients (15.3%)	
Shepherd *et al.*, 2004 (19)	Case series	Bariatric surgery, high risk	100	UFH low-dose IV infusion, target anti-FXa 0.15–0.2 units/ml	GCS or Ace™ bandage	BMI >35	Anti-FXa levels, symptomatic VTE (MB)		Average anti-FXa 0.15 U/ml (95% CI: 0.10–0.29); no VTE (two events)	[31]
Shepherd *et al.*, 2003 (700)	Case series	Bariatric surgery	100	s.c. UFH, target anti-FXa 0.11–0.25 units/ml	GCS or Ace bandage	BMI >35	Symptomatic VTE (MB)		0.4% (1%)	[32]

b.i.d.: Twice per day; EA: Early ambulation; FXa: Factor Xa; GCS: Graduated compression stocking; HC: Historical control; HRIVCF: Inferior venous filter placement in high-risk patients; IPC: Intermittent pneumatic compression; IVCF: Inferior vena cava filter; MB: Major bleed; NR: Not reported; NS: Not significant; q.d.: Once daily; RCT: Randomized controlled trial; s.c.: Subcutaneously; U: Units; UFH: Unfractionated heparin; VTE: Venous thromboembolism.

Data taken from [64].