Dosage of Anticoagulants in Obesity: Recommendations Based on a Systematic Review

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Abstract

Anticoagulants are frequently used as thromboprophylaxis and in patients with atrial fibrillation (AF) or venous thromboembolism (VTE). While obesity rates are reaching epidemic proportions worldwide, the optimal dosage for obese patients has not been established for most anticoagulants, including low-molecular-weight heparin (LMWH), non–vitamin K antagonist oral anticoagulants (NOAC), and pentasaccharides (fondaparinux). The aim of the present systematic review was to summarize the current knowledge and provide recommendations on dosage of LMWH, NOAC, and fondaparinux in obese patients (body mass index [BMI] $\geq$ 30 kg/m^2 or body weight $\geq$ 100 kg). Based on a systematic search in PubMed and Embase, a total of 72 studies were identified. For thromboprophylaxis with LMWH in bariatric surgery ($n = 20$ studies), enoxaparin 40 mg twice daily, dalteparin 5,000 IE twice daily, or tinzaparin 75 IU/kg once daily should be considered for patients with BMI $\geq$ 40 kg/m^2. For thromboprophylaxis with LMWH in nonbariatric surgery and in medical inpatients ($n = 8$ studies), enoxaparin 0.5 mg/kg once or twice daily or tinzaparin 75 IU/kg once daily may be considered in obese patients. For treatment with LMWH ($n = 18$ studies), a reduced weight-based dose of enoxaparin 0.8 mg/kg twice daily should be considered in patients with BMI $\geq$ 40 kg/m^2, and no dose capping of dalteparin and tinzaparin should be applied for body weight $<$ 140 kg. As regards NOAC, rivaroxaban, apixaban, or dabigatran may be used as thromboprophylaxis in patients with BMI $<$ 40 kg/m^2 ($n = 4$ studies), whereas rivaroxaban and apixaban may be administered to obese patients with VTE or AF, including BMI $>$ 40 kg/m^2, at standard fixed-dose ($n = 20$ studies). The limited available evidence on fondaparinux ($n = 3$ studies) indicated that the treatment dose should be increased to 10 mg once daily in patients weighing $>$ 100 kg.

Keywords
- Anticoagulants
- thromboprophylaxis
- obesity

According to the World Health Organization, the prevalence of obesity worldwide has almost tripled since 1975, and more than 650 million were classified as obese in 2016.[1] A person with a body mass index (BMI) $\geq$ 30 kg/m^2 is typically considered obese, whereas morbid obesity is defined as BMI $\geq$ 40 kg/m^2.[1] Undoubtedly, obesity is associated with an increased risk of a broad range of acute and chronic diseases, including venous thromboembolism (VTE) and atrial fibrillation (AF).[2,3] Anticoagulants play a pivotal role in the treatment of VTE, as well as in the prevention of stroke, and systemic embolism in patients suffering from AF, and various agents are routinely prescribed, including vitamin K antagonists (VKA), unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), non–vitamin K antagonist oral anticoagulants (NOAC) and pentasaccharides (fondaparinux).

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Obesity may constitute a major challenge in the dosing of anticoagulants. Whereas VKA and UFH are commonly administered and monitored according to biochemical measures, such as the international normalized ratio (INR) or activated partial thromboplastin time (aPTT), LMWH, NOAC, and fondaparinux are administered as fixed doses or according to body weight. Potentially, such nonmonitored dosing regimens may lead to either an underdosing or excessive exposure to the drug in patients with an aberrant body weight. In addition, obesity itself may presumably have a considerable effect on the pharmacokinetics of the drugs.[4] In view of these concerns, one may hypothesize that obese patients need a different dose of anticoagulants to maintain optimal clinical and biochemical effect and safety of the drug. The aim of the present study was, therefore, to systematically summarize the current knowledge on efficacy and safety of LMWH, NOAC, and fondaparinux used for prophylaxis or treatment in obese individuals and to provide recommendations on dosage of these drugs in obese patients.

Methods

PubMed and Embase were utilized to identify relevant articles. The search string is presented in ►**Table 1**. PubMed was initially searched on June 17, 2019, and Embase was searched on June 24, 2019. Both searches were repeated on November 20, 2019, to include the most recent published studies. We used the following eligibility criteria: (1) individuals with body weight $\geq$ 100 kg or with BMI $\geq$ 30 kg/m^2; (2) original data; (3) English language; (4) information on type and dose for LMWH; (5) evaluation of clinical efficacy, biochemical efficacy (antifactor Xa), and/or safety (bleeding); and (6) adults (age $>$ 18 years). The following exclusion criteria were implemented: (1) guidelines or surveys on clinical practice, (2) editorials or comments, (3) in vitro or animal studies, (4) conference abstracts or case reports with $\leq$ 5 cases, (5) studies on pregnant/postpartum women, (6) studies investigating UFH or warfarin alone, and (7) studies evaluating the surgery procedure as primary goal.

The first 50 abstracts were screened independently by all three authors, and the remaining abstracts by S.A.M. or A.A. The first 30 articles suitable for full-text assessment were evaluated by all three authors and the remaining by S.A.M. or A.A. All cases of doubt were discussed in plenum to reach consensus. No statistical analyses were performed.

Results and Discussion

A total of 1,571 unique records were identified in the search, and 6 additional records were identified from related

Table 1 Search strings

Database	Obesity	LMWH, NOAC, or fondaparinux		
		LMWH	NOAC	Fondaparinux
PubMed	obesity OR obese OR morbid obesity OR overweight obesity OR overweight OR "obesity" [Mesh] OR "overweight" [Mesh] OR "obesity, morbid" [Mesh]	LMWH OR "heparin, low-molecular-weight" [Mesh] OR low molecular weight heparin OR "enoxaparin" [Mesh] OR enoxaparin OR "tinzaparin" [Mesh] OR tinzaparin OR "dalteparin" [Mesh] OR dalteparin	antithrombins OR "antithrombins" [Mesh] OR dabigatran OR "dabigatran" [Mesh] OR dabigatran etexilate OR "edoxaban" [Supplementary Concept] OR edoxaban OR "apixaban" [Supplementary Concept] OR apixaban OR factor Xa inhibitor OR "rivaroxaban" [Mesh] OR rivaroxaban OR direct oral anticoagulants OR DOAC OR new oral anticoagulants OR NOAC	"Fondaparinux" [Mesh] OR fondaparinux
Embase[a]	obesity OR obese OR (morbid AND obesity) OR (overweight AND obesity) OR overweight OR "obesity"/exp OR "morbid obesity"/exp	"dalteparin"/exp OR "tinzaparin"/exp OR "enoxaparin"/exp OR "low molecular weight heparin"/exp OR dalteparin OR tinzaparin OR enoxaparin OR (low AND molecular AND weight AND heparin) OR LMWH	NOAC OR "new oral anticoagulant" OR "new oral anticoagulant"/exp OR "blood clotting factor 10a inhibitor"/exp OR "blood clotting factor 10a inhibitor" OR "rivaraxoban"/exp OR "rivaraxoban" OR "apixaban"/exp OR apixaban OR "edoxaban"/exp OR edoxaban OR "dabigatran etexilate"/exp OR "dabigatran etexilate" OR "dabigatran"/exp OR "dabigatran" OR OR "fondaparinux")	

Abbreviations: LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulants.
[a]Filters applied in Embase: "human"/de AND ("article"/it OR "article in press"/it OR "letter"/it).

reviews (►**Fig. 1**). After review of titles and abstracts, 237 records were left for full-text assessment, and a total of 72 studies were subsequently included in the present systematic review. The records were subdivided into (1) LMWH as thromboprophylaxis in bariatric surgery, nonbariatric surgery, or medical or trauma inpatients; (2) LMWH as treatment; (3) NOAC as thromboprophylaxis; (4) NOAC as treatment; and (5) fondaparinux as thromboprophylaxis or treatment.

Low-Molecular-Weight Heparin Used for Prophylaxis

In nonobese patients, LMWH is recommended to be administered as a fixed dose for thromboprophylaxis in high-risk situations (enoxaparin, 40 mg once daily; dalteparin, 5,000 IU once daily; and tinzaparin, 4,500 IU once daily). In the current Summary of Product Characteristics, a few precautions are stated for obese patients. For enoxaparin, it is stated that the safety and efficacy in obese patients have not been fully determined, and that the need for dose adjustment is uncertain.[5] For tinzaparin, it is stated that a dose of 50 IU/kg may be administered to patients with very high body weight although the term "very high body weight" remains unspecified.[6] For dalteparin, it is advised that plasma anti-Xa is measured in morbidly obese patients.[7] Clearly, such vague recommendations leave room for improvement.

Prophylaxis in Bariatric Surgery

In our search, we identified 20 studies evaluating LMWH as thromboprophylaxis in bariatric surgery (►**Table 2**). Among 15 bariatric studies utilizing enoxaparin, one study was a randomized control trial (RCT), five were prospective cohort studies, and nine studies were retrospective cohort studies based on medical chart review. For dalteparin, one prospective cohort study and three retrospective bariatric studies were identified, whereas only a single retrospective cohort

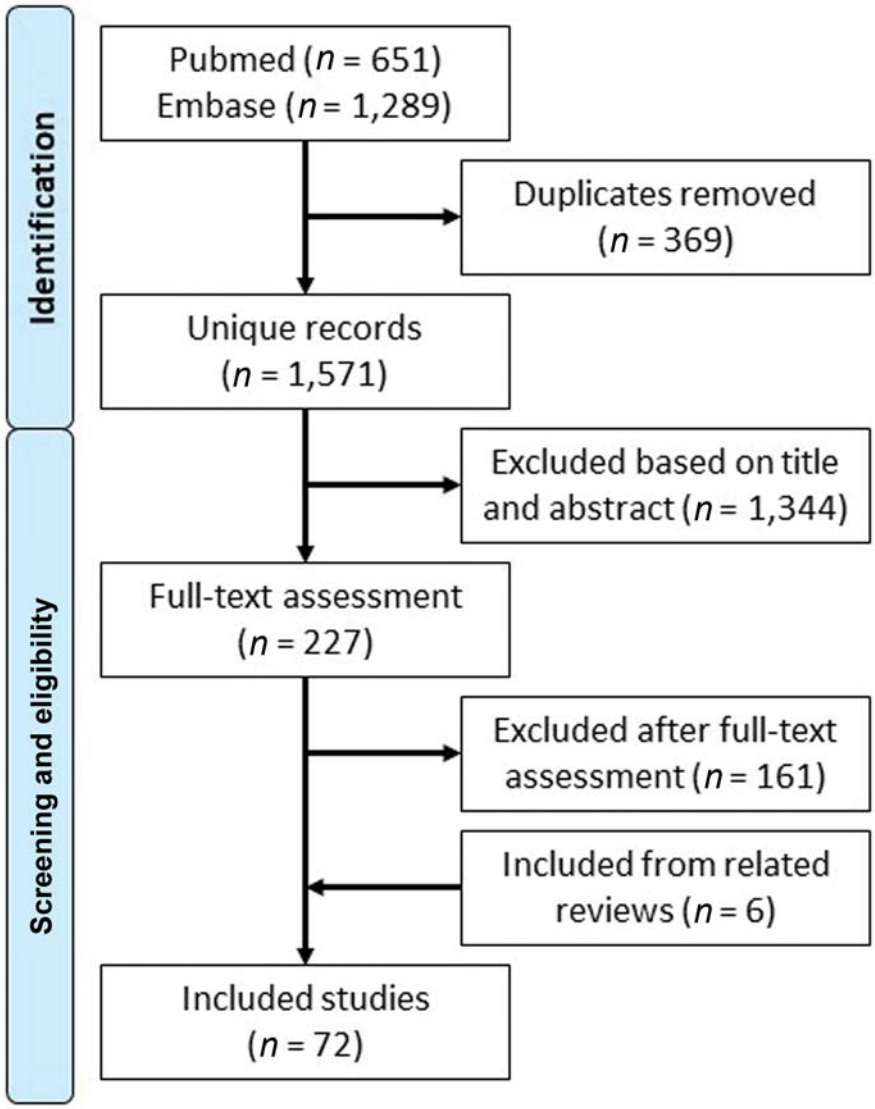

Fig. 1 Flowchart describing the selection process of articles.

Table 2 Studies investigating low-molecular-weight heparin for prophylaxis in obese patients after bariatric and nonbariatric surgery and in nonsurgical inpatients

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
Bariatric surgery, enoxaparin ($n = 16$)					
Randomized controlled trials					
2016, Steib et al[8]	RCT BMI > 40 (mean BMI 48 kg/m^2), $n = 135$ Follow-up: 30 d	Enoxaparin 40 mg once daily, $n = 44$ vs. enoxaparin 60 mg once daily, $n = 44$ vs. enoxaparin 40 mg twice daily, $n = 47$ Minimum duration 10 d, initiated on the evening before surgery	Clinical efficacy DVT Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.3–0.5 IU/mL Safety Perioperative bleeding	Clinical efficacy No events Biochemical efficacy 40 once vs. 60 once vs. 40 twice; Within range: 12.8 vs. 56.4% vs. 26.2% (60 once significantly higher level, $p = 0.001$) Safety 40 once vs. 60 once vs. 40 twice; Bleeding events: 1 vs. 2 vs. 6, $p = 0.19$	A significantly greater proportion reached anti-Xa range with 60 mg enoxaparin. No significant differences in bleeding risks between dosing regimens
Prospective cohort studies					
2008, Borkgren-Okonek et al[13]	Prospective cohort study BMI ≤ 50 (mean BMI = 44.9), $n = 124$ BMI > 50 (mean BMI 57.4), $n = 99$ Follow-up: 3 mo	Enoxaparin 40 mg twice daily (BMI ≤ 50) or 60 mg twice daily (BMI > 50) (during hospitalization) + 40 mg once daily (BMI ≤ 50) or 60 mg once daily (BMI > 50) for 10 d after discharge	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.4 IU/mL. Safety Bleeding	Clinical efficacy VTE: 1 case (40 mg), postoperative day 37 Biochemical efficacy 40 vs. 60 mg Within range: 78.9 vs. 69.1%. Supratherapeutic: 0 vs. 16.5% Subtherapeutic: 21.1 vs. 14.4% Safety Major bleeding: 4 cases (40 mg) + 1 case (60 mg) Minor bleeding: 3 cases	A BMI-stratified, extended enoxaparin dosing regimen provided well-tolerated, effective prophylaxis against VTE in patients undergoing gastric bypass surgery
2019, Brunetti et al[12]	Prospective cohort study Mean BMI = 44.7, $n = 60$ Follow-up: 30 d from discharge	Enoxaparin, 40 mg twice daily, $n = 16$, initiated 2–3 h preoperatively, duration NR or UFH, 5,000 units (< 120 kg) or 7,500 units120	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.1–0.5 IU/mL.	Clinical efficacy No events Biochemical efficacy Enoxaparin vs. UFH; Within range: 93.8 vs. 4.5%, $p < 0.0001$	In obese, patients receiving enoxaparin achieved anti-Xa range more often vs. UFH, but more bleedings were

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Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
		kg) × 3 daily, $n = 44$, initiated 2–3 h preoperatively, duration NR	Safety Bleeding	Safety Enoxaparin vs. UFH Major bleeding: 1 case vs. 0 cases Minor bleeding: 87.5 vs. 27.3%, $p < 0.0001$	observed with enoxaparin
2015, Celik et al[9]	Prospective cohort study < 110 kg, $n = 17$ 110–150 kg, $n = 18$ > 150 kg, $n = 16$ Follow-up: 8–16 d from surgery	Enoxaparin, 40 mg twice daily for 14 d	Clinical efficacy Thrombotic events Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL Safety Bleeding	Clinical efficacy No events Biochemical efficacy < 100 kg vs. 110–-150 kg vs. > 150 kg; Within range: 64.7 vs. 94.4 vs. 62.5%, $p = 0.054$ Supratherapeutic: 35.3 vs. 5.6 vs. 0%, $p = 0.006$ Subtherapeutic: 0 vs. 0 vs. 37.5%, $p = 0.001$ Safety Major bleeding: no events Minor bleeding: < 110 kg: 5 events; 110–150 kg: 2 events; > 150 kg: 1 event, $p = 0.157$. All with anti-Xa levels within range	Patients > 150 kg were less likely to achieve anti-Xa range than the other weight groups; fixed 40-mg may not be sufficient in patients > 150 kg. No major bleeding or VTE observed
2017, Gelikas et al[10]	Prospective cohort study BMI ≥ 35 + ≥ 2, comorbid conditions, or BMI ≥ 40 (mean BMI = 43.1), $n = 54$ Follow-up: 3 d postoperatively	Enoxaparin 40 mg once daily, $n = 31$, duration NR or enoxaparin 60 mg once daily, $n = 23$, duration NR	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.5 U/mL Safety Bleeding	Clinical efficacy No events Biochemical efficacy 40-mg vs. 60-mg; Mean anti-Xa: 0.247 U/mL vs. 0.346 U/mL, $p = 0.001$. Within range: 80.6 vs. 91.3% Supratherapeutic: 0 vs. 8.7% Subtherapeutic: 19.4 vs. 0%.	Both enoxaparin dosing regimens studied were reasonable choices for VTE prophylaxis after bariatric surgery, but 60 mg was superior to 40 mg in reaching anti-Xa range

Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
				C^2 test: $p = 0.016$ Safety 60 mg: 1 excessive bleeding during surgery	
2013, Khoursheed et al[11]	Prospective cohort study Mean BMI = 44.59, $n = 39$ Follow-up: 6 wk	Enoxaparin, 40 mg once daily, initiated preoperatively until 5 d postoperatively	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.6 U/mL Safety Bleeding	Clinical efficacy No events in study population. 1 fatal PE in all dept.'s bariatric patients (0.09%) Biochemical efficacy Day 2: Mean anti-Xa: 0.19 U/mL Within range: 46.1% Day 5: Mean anti-Xa: 0.13 U/mL Within range: 41% Safety No bleeding	Enoxaparin 40 mg once daily may be insufficient in obese bariatric patients with less than 50% reaching anti-Xa range
Retrospective cohort studies (chart reviews)					
2008, Escalante-Tattersfield et al[16]	Retrospective cohort study (chart review) BMI $\geq 35 + \geq 2$ comorbid conditions, or BMI $\geq$ 40 (mean BMI 49), $n = 618$ Follow-up: up to 52 wk from surgery	UFH 5,000 U $\times$ 3 (first 24 h after surgery) + enoxaparin, 40 mg twice daily (24 h after surgery until discharge)	Clinical efficacy VTE Biochemical efficacy NR Safety Bleeding episodes, HIT	Clinical efficacy DVT: 0.16% (1 event) Safety Gastrointestinal bleeding: 1.6% (6 events) Clinically significant bleeding: 0 events HIT: 0 events	The treatment regimen seemed effective in obese patients with few events of VTE and bleeding
2008, Ojo et al[21]	Retrospective cohort study (chart review) BMI $\geq$ 50 and comorbidity, $n = 84$ BMI $\geq$ 60, $n = 43$ (mean BMI = 58) Follow-up: 2 wk	Enoxaparin, 40 mg twice daily for 2 wk or enoxaparin, 60 mg twice daily for 2 wk	Clinical efficacy NR Biochemical efficacy NR Safety Bleeding or decrease in hematocrit	Safety No major bleedings. No decrease in hematocrit to critical levels	Both enoxaparin regimens were safe in obese with BMI $\geq$ 50
2007, Paige et al[22]	Retrospective cohort study (chart review) BMI $\geq$ 35 and	Enoxaparin 1 mg/BMI-unit twice daily initiated	Clinical efficacy NR Biochemical efficacy	Biochemical efficacy Transfused (data from 58%) vs. not-transfused	Transfusions rate in obese did not vary

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Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	comorbidity or BMI $\geq$ 40, total $n = 102$ (mean BMI = 49). Follow-up: NR	6 h preoperatively, duration NR	Anti-Xa (peak, steady state). Range: 0.1–0.2 IU/mL Safety Blood transfusions (packed red blood cells, PRBCs)	(data from 82%); Mean anti-Xa: 0.13 IU/mL vs. 0.16 IU/mL, $p = 0.7$ Safety Transfusion rate: 11.7%. (transfused, n = 12; not transfused, n = 90) Transfused vs. not transfused, BMI: 48.9 vs. 48.7, $p = 0.9$	significantly with BMI or mean anti-Xa-levels
2008, Raftopoulos et al[15]	Retrospective cohort study (chart review) Mean BMI = 46.8, $n = 308$ Follow-up: a minimum of 1 mo	Year 2003–2005: enoxaparin 30 mg twice daily during hospitalization, $n = 132$ or year 2006–2007: enoxaparin 30 mg twice daily followed by 40 mg once daily for 10 d after discharge, $n = 176$	Clinical efficacy VTE within 30 d 30-d morbidity (death, anastomotic leak, hemorrhage, VTE, small bowel obstruction, cardiac/renal/pulmonary complication) Biochemical efficacy NR Safety Bleeding episodes within 30 d	Clinical efficacy In-hospital vs. extended; VTE-rates: 4.5 vs. 0%, $p = 0.006$ All morbidity: 12.1 vs. 1.1%, $p < 0.0001$ Death: 0 vs. 0%, $p =$ NS Safety In-hospital vs. extended; Significant bleeding: 5.3 vs. 0.56%, $p = 0.02$	Extended prophylaxis in obese patients was superior to prophylaxis during hospitalization only
2017, Rottenstreich et al[14]	Retrospective cohort study (chart review) Mean BMI = 41.8, $n = 4{,}386$ Follow-up, mean: 26 mo	Enoxaparin 40 mg once daily during hospitalization, $n = 3{,}843$ or enoxaparin 40 mg once daily for 1–4 wk after discharge, $n = 543$	Clinical efficacy Thrombotic events (PSMVT, DVT, PE) Biochemical efficacy NR Safety NR	Clinical efficacy Standard regimen vs. extended, events; DVT: 12 vs. 0, $p = 0.38$ PE: 6 vs. 0, $p = 0.55$ PSMVT: 16 vs. 0, $p = 0.25$ Any thrombotic event: 34 vs. 0, $p = 0.02$	Significantly fewer thrombotic events in patients receiving extended enoxaparin
2008, Rowan et al[19]	Retrospective cohort study (chart review) Mean BMI = 48.5, $n = 52$ Follow-up: NR	Former time period: enoxaparin 30 mg twice daily, $n = 19$, mean BMI 48.4 or Latter time period: enoxaparin, 40 mg	Clinical efficacy NR Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.18–0.44 U/mL	Biochemical efficacy 30 vs. 40 mg Mean anti-Xa (U/mL): 0.08 vs. 0.15 Within range: 9.1 vs. 41.7%, $p = 0.115$	More than half of the patients receiving 40 mg every 12 h failed to reach therapeutic

Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
		twice daily $n = 33$, mean BMI = 48.4	Safety NR		levels. No levels were supratherapeutic
2002, Scholten et al[17]	Retrospective cohort study (chart review) Mean BMI 50.6, $n = 481$ Follow-up: at least 6 mo	Former time period: Enoxaparin 30 mg twice daily until fully ambulatory/discharge, $n = 92$ or Latter time period: enoxaparin 40 mg twice daily until fully ambulatory/discharge, $n = 389$	Clinical efficacy VTE Biochemical efficacy NR Safety Bleeding	Clinical efficacy 30-mg vs. 40-mg; VTE events: 5.4 vs. 0.6%, $p = 0.01$ Safety 30 vs. 40 mg; bleeding: 1 vs. 1, p = NS	Without increasing risk of bleeding, 40 mg enoxaparin was superior to 30 mg in protection against VTE in obese
2008, Simone et al[20]	Retrospective cohort study (chart review) Mean BMI = 48.2, $n = 40$ Follow-up: until discharge	Enoxaparin 40 mg twice daily until discharge, $n = 24$ or enoxaparin 60 mg twice daily until discharge, $n = 16$	Clinical efficacy NR Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.18–0.44 U/mL Safety Bleeding episodes	Biochemical efficacy 40-mg vs. 60-mg Subtherapeutic: 44 vs. 0%, $p = 0.02$. Supratherapeutic: 0 vs. 57%, $p = 0.02$ Mean anti-Xa: 0.21 vs. 0.43 U/mL, $p < 0.001$ Safety Overall: 1 bleeding event (40 mg)	The majority of patients treated with enoxaparin 60 mg twice daily reached supratherapeutic levels, whereas almost half of patients treated with 40 mg twice daily were subtherapeutic
2012, Singh et al[18]	Retrospective cohort study (chart review) Mean BMI = 47.8, $n = 170$ Follow-up: at least 2 y	BMI-based enoxaparin. BMI < 40: 30 mg twice daily, $n = 11$ BMI = 41–49: 40 mg twice daily, $n = 145$ BMI 50–59: 50 mg twice daily, $n = 9$ BMI > 59: 60 mg twice daily, $n = 5$ + a single similar BMI-based dose administered 1 h preoperatively Duration: NS	Clinical efficacy VTE Biochemical efficacy NR Safety Bleeding	Clinical efficacy No VTE Safety Postoperative bleeding rate: 2.9% (4 in 40-mg group, 1 in 60-mg group)	A BMI-based dosing strategy seems efficient in preventing thromboembolic events

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Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
Bariatric surgery, dalteparin ($n = 4$)					
Prospective cohort studies					
2018, Gaborit et al[26]	Prospective cohort study BMI $\geq 35 + \geq 2$ comorbid conditions, or BMI ≥ 40 (mean BMI = 43.3), $n = 113$ Follow-up: 3 mo	Dalteparin, 5,000 IU twice daily for 14 d	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL. Safety Bleeding	Clinical efficacy No events Biochemical efficacy Median peak level 0.19 IU/mL (0.13–0.26 IU/mL) Within range: 48% Supratherapeutic: 0.08% Subtherapeutic: 51.92% Safety Major bleeding: no events Minor bleeding: 1 event (subtherapeutic anti-Xa)	Majority of obese did not achieve therapeutic levels with dalteparin. No major bleedings or VTE events observed
Retrospective cohort studies (chart reviews)					
2019, Leeman et al[23]	Retrospective cohort study (chart review) Mean BMI = 43.3, $n = 3,319$ Follow-up: 3 mo	Dalteparin, 5,000 IU once daily for 14 d, $n = 2,599$ or dalteparin, 5,000 IU once daily during hospitalization only, $n = 720$	Clinical efficacy VTE Biochemical efficacy NR Safety Postoperative hemorrhage within 1 mo	Clinical efficacy VTE events: 0.07% (extended treatment group) Safety Bleeding: 34/2,599 (1.3%, 95% CI 0.9–1.8%) for regimen I and 8/720 (1.1%, 95% CI 0.5–2.2%) for regimen II ($p = 0.675$)	Short term use of standard fixed-dose thromboprophylaxis (during hospitalization only) in metabolic surgery is safe
2010, Magee et al[24]	Retrospective cohort study (chart review) Mean BMI = 47.9, $n = 735$ Follow-up: a minimum of 6 mo	Dalteparin 2,500 IU once daily preoperatively + 5,000 IU once daily postoperatively for 7 d (laparoscopic procedure) or 21 d (gastric banding)	Clinical efficacy Symptomatic VTE and 30- and 90-d mortality rate Biochemical efficacy NR Safety Bleeding, HIT	Clinical efficacy VTE events: 0 Mortality rate: 0% Safety Bleeding: 3 events HIT: 0 events	The dalteparin regimen seems effective with no thrombotic events and with low incidence of bleeding

Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
2010, Simoneau et al[25]	Retrospective cohort study (chart review) BMI $\geq$ 35 with comorbidity or BMI $\geq$ 40 (mean BMI 53.7), $n = 135$ Follow-up: NR	Dalteparin, 7,500 IU once daily, duration: NR	Clinical efficacy Thrombotic events Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL Safety Bleeding	Clinical efficacy No events Biochemical efficacy Within range: 60.0% Supratherapeutic: 9.6% Subtherapeutic: 30.4% Patients > 180 kg ($n = 16$) had mean anti-Xa below target. Safety Bleedings: 3 events, but no association with anti-Xa level	The 7,500 IU dalteparin dosage is appropriate for the majority of morbidly obese patients undergoing bariatric surgery. Very high body weight (> 180 kg) may need a higher dose to reach range
Bariatric surgery, tinzaparin ($n = 1$)					
Retrospective studies (chart reviews)					
2018, Tseng et al[27]	Retrospective cohort study (chart review) Median BMI = 47.9, $n = 1,212$ Follow-up: 30 d	Tinzaparin, 75 IU/kg once daily starting on postoperative day 1 for 10 d	Clinical efficacy VTE Biochemical efficacy Anti-Xa (trough level, steady state) Safety Bleeding	Clinical efficacy VTE rates In-hospital: 0.2% Follow-up: 0.5% Biochemical efficacy Anti-Xa: < 0.4 IU/mL in all patients Safety Major bleeding rate In-hospital: 1.8% Follow-up: 1.6%	Extended thromboprophylaxis with weight-adjusted tinzaparin appears to be a safe strategy after bariatric surgery with slow rates of VTE and major bleeding
Nonbariatric surgery, enoxaparin ($n = 2$)					
Prospective cohort studies					
2017, Al Otaib et al[29]	Prospective cohort study BMI $\geq$ 35 (median BMI 40.5), $n = 50$ Follow-up: NR Thromboprophylaxis, mixed surgery	Enoxaparin, 0.5 mg/kg once daily, duration: NR	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state) Range: 0.2–0.6 IU/mL Safety Major and minor bleeding; HIT	Clinical efficacy No events Biochemical efficacy Within range: 88% Supratherapeutic: 4% Subtherapeutic: 8% Safety No events	Weight-based enoxaparin dose led to the anticipated anti-Xa levels in most of the morbidly obese patients without any evidence of major side effects. No VTE or bleeding were observed

(*Continued*)

Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
Retrospective cohort studies (chart reviews)					
2011, Ludwig et al[30]	Retrospective cohort study (chart review) BMI $\geq$ 35 or $\geq$ 150 (mean BMI: 46.4), $n = 23$ Follow-up: 30 d from discharge Thromboprophylaxis, mixed surgery	Enoxaparin, 0.5 mg/kg twice daily during surgical intensive care (followed by 30 or 40 mg twice daily)	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL Safety Bleeding; HIT	Clinical efficacy VTE: 1 DVT, maybe pre-existing (anti-Xa-level: 0.38 IU/mL on 70 mg enoxaparin) Biochemical efficacy Mean anti-Xa: 0.34 IU/mL Within range: 91% ($n = 21$) Supratherapeutic: $n = 2$ Subtherapeutic: $n = 0$ Safety Minor bleeding: 1 event No major bleeding or HIT	Weight-based dosing with enoxaparin in morbidly obese surgical intensive care patients was effective in achieving appropriate anti-factor Xa levels. It also reduced the rate of VTE below expected levels and no additional adverse effects were reported
Medical or trauma inpatients, enoxaparin ($n = 5$)					
Randomized controlled trials					
2017, Miranda et al[31]	RCT Medical inpatients, BMI $\geq$ 30 (mean BMI = 37.8), $n = 91$ Follow-up: 14 d	Enoxaparin 40 mg once daily for 14 d, $n = 45$ vs. enoxaparin 60 mg once daily for 14 d, $n = 46$	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.32–0.54 IU/mL Safety Major/minor bleeding	Clinical efficacy No events Biochemical efficacy 40 vs. 60 mg; Within range: 31 vs. 69%, $p = 0.007$. Supratherapeutic: NR Subtherapeutic: 64 vs. 36%, $p = 0.001$. Safety One fatal major bleeding (ulcer) (40 mg) 2 minor bleedings in each group	In medically obese inpatients, thromboprophylaxis with enoxaparin 60 mg provides higher control of anti-Xa activity, without more bleeding complications than the standard enoxaparin regimen
Prospective cohort studies					
2013, Bickford et al[33]	Prospective cohort study Trauma patients, BMI $\geq$ 30 (median BMI = 35.3), $n = 86$ Follow-up, mean: 9.5 d	Enoxaparin, 0.5 mg/kg twice daily, duration: NR	Clinical efficacy VTE (ultrasound screening of all patients) Biochemical efficacy Anti-Xa (peak, steady	Clinical efficacy PE: 0 (0%) DVT: 18 (21%), 16 found before start of enoxaparin. Biochemical efficacy	In obese trauma patients, weight-based enoxaparin is an efficacious regimen that provides adequate VTE prophylaxis, as

Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
			state). Range: 0.2–0.6 U/mL Safety Bleeding	Within range: $n = 74$ (86%) Supratherapeutic: $n = 8$ Subtherapeutic: $n = 4$ Safety No bleeding events	measured by anti-Xa levels, and appears to be safe without bleeding complications
2012, Freeman et al[34]	Prospective cohort study Medical inpatients, BMI $\geq$ 40 (average BMI 62.1), $n = 31$ Follow-up, mean: 3 d	Enoxaparin fixed-dose, 40 mg once daily, $n = 11$ or Enoxaparin low-dose, 0.4 mg/kg once daily, $n = 9$ or Enoxaparin high-dose, 0.5 mg/kg once daily, $n = 11$ Duration: NR	Clinical efficacy Symptomatic DVT or PE Biochemical efficacy Anti-Xa (peak, steady-state). Range: 0.2–0.5 IU/mL Safety Bleeding and HIT	Clinical efficacy No events Biochemical efficacy Subtherapeutic levels, fixed vs. low-dose vs. high dose: 82 vs. 36 vs. 13%, $p < 0.001$ One case supratherapeutic (low dose). Safety No events	In extremely obese, medically ill patients, enoxaparin 0.5 mg/kg once daily is superior to fixed-dose and lower-dose enoxaparin for the achievement of anti-Xa range
2010, Rondina et al[35]	Prospective cohort study Medical inpatients, BMI $\geq$ 35 (median BMI = 48.1), $n = 28$ Follow-up: until hospital discharge	Enoxaparin, weight-based 0.5 mg/kg once daily for 2 consecutive days	Clinical efficacy VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.6 U/mL Safety Bleeding episodes; HIT	Clinical efficacy No events Biochemical efficacy Average peak anti-Xa: 0.25 U/mL, range 0.08–0.59 U/mL) Safety No events	A weight-based dose resulted in peak anti-Xa levels within or near recommended range for thromboprophylaxis, without any evidence of excessive anti-Xa activity
2015, Rostas et al[32]	Prospective cohort study Trauma patients BMI $\geq$30, $n = 14$ BMI $<$ 30, $n = 14$ Mean BMI 32.3. Follow-up: NR	Enoxaparin, 30 mg twice daily, duration: NR	Clinical efficacy NR Biochemical efficacy Anti-Xa (trough level before 4th dose); subtherapeutic level defined as $<$ 0.1 IU/mL Safety NR	Biochemical efficacy Subtherapeutic trough level: obese vs. non-obese: 65% vs. 53%, $p = 0.73$	An enoxaparin dose of 30 mg twice daily is not sufficient for the majority of adult trauma patients in the intensive care unit, regardless of BMI
Medical or trauma inpatients, tinzaparin ($n = 1$)					
2002, Hainer et al[36]	Pharmacodynamic study Volunteers, 101–165 kg (mean weight 129.6 kg), $n = 37$ Control	Single dose tinzaparin 75 IU/kg or Control subjects: Tinzaparin 4,500 IU (adjusted for weight and scaled to 75 IU/kg to compare;	Clinical efficacy NR Biochemical efficacy Anti-Xa (peak, steady state): Amax, AUC Anti-IIa activity	Biochemical efficacy Obese vs. controls Anti-Xa activity: AUC: 3.29 (95% CI 3.017–3.565) vs. 2.36 (2.164–2.556) Amax:	In general, weight-adjusted dosing did not differ significantly between obese and normal weight (only anti-

(*Continued*)

Table 2 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up	Treatment Medication, daily dose, and duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	subjects < 100 kg from prior studies, $n = 27$ Follow-up: 8 d from second dose	treatment dose, see ►**Table 3**)	Safety Bleeding events	0.34 (0.303–0.375) vs. 0.30 (0.281–0.319) Anti-IIa activity: AUC: 1.21 (95% CI 1.088–1.340) vs. 0.77 (0.680–0.860) Amax: 0.12 (0.103–0.133) vs. 0.10 (0.088–0.112) Safety No major bleeding events	Xa AUC significantly higher in obese)

Abbreviations: Amax, maximum observed activity; AUC, area under the plasma activity curve; BMI, body mass index (kg/m^2); CI, confidence interval; DVT, deep venous thrombosis; HIT, heparin-induced thrombocytopenia; NR, not reported; NS, nonsignificant PE, pulmonary embolism; PSMVT, portal-splenic-mesenteric venous thrombosis; RCT, randomized, controlled trial; TBW, total body weight; UFH, unfractionated heparin; VTE, venous thromboembolism.

study based on medical chart review was found for tinzaparin.

The RCT by Steib et al compared enoxaparin 40 mg once daily, 40 mg twice daily, and 60 mg once daily in 135 morbidly obese patients with BMI > 40 kg/m^2 (mean BMI, 48 - kg/m^2) undergoing bariatric surgery.[8] A significantly larger proportion of patients reached target anti-Xa with 60 mg once daily. Notably, the same range of 0.3 to 0.5 IU/mL was used for all regimens although one group received two daily doses. Nevertheless, no thrombotic events and only a few bleeding episodes were observed in any group during 30 days of follow-up.

Overall, the five prospective cohort studies on enoxaparin included a low number of obese patients ($n = 39$–223), and, if any, only a few cases of VTE and bleedings were observed.[9–13] Therefore, their conclusions mainly relied on biochemical measures. Three studies, collectively, seemed to agree on the notion that 40 mg once or twice daily is associated with a relatively low proportion of patients reaching the biochemical target, especially in patients > 150 kg.[9–11] However, Brunetti et al did observe that 40 mg twice daily was sufficient in the majority of patients, but a wider anti-Xa range of 0.1 to 0.5 IU/mL was utilized in this study.[12] The largest prospective study by Borkgren-Okonek et al included 223 patients and found satisfactory anti-Xa levels and only a single VTE event with enoxaparin 40 mg twice daily during hospitalization, followed by 40 mg once daily for 10 days after discharge for patients with BMI ≤ 50 kg/m^2 and 60 mg once daily for patients with BMI > 50 kg/m^2.[13]

Nine retrospective studies, based on medical chart review, evaluating enoxaparin, were found. Rottenstreich et al performed the largest study, which included 4,386 obese patients with a mean BMI of 41.8 kg/m^2.[14] The majority received thromboprophylaxis (40 mg once daily) during hospitalization only, but 543 unspecified high-risk patients received extended prophylaxis for 1 to 4 weeks. During a follow-up of 26 months, no thrombotic events were observed in the patients receiving extended prophylaxis. Similarly, Raftopoulos et al found that 40 mg once daily for 10 days after discharge was more clinically effective and safer than in-hospital prophylaxis only.[15] Unfortunately, the two regimens of the latter study were used during two separated time periods, and this circumstance hinders their direct comparison due to possible selection bias. On the contrary to these studies with extended treatment, Escalante-Tattersfield et al found no thrombotic events and a low bleeding rate with 40 mg twice daily during hospitalization only.[16] Scholten et al found 40 mg twice daily more clinically effective than 30 mg twice daily until discharge in 481 patients with mean BMI of 50.6 kg/m^2 without increased risk of bleeding[17]; indeed, the thrombotic event rate was 5.4% with 30 mg twice daily and 0.6% with 40 mg twice daily. Unfortunately, the dosing was not randomized, and the two regimens were again utilized during two separate time periods. Finally, Singh et al found no thrombotic events in patients treated with a BMI-based dose (30–60 mg).[18] A single dose was administered 1 hour before surgery followed by twice daily administrations from the

first postoperative day (total number of treatment days unspecified).

Two of the retrospective studies primarily evaluated biochemical endpoints, and both studies found 40 mg twice daily insufficient in patients with mean BMI around 48 kg/m^2.[19,20]

Ojo et al primarily evaluated safety of enoxaparin (40 or 60 mg twice daily) and found that both doses were safe in patients with BMI $\geq$ 50 kg/m^2.[21] Similarly, Paige et al found a strategy of 1 mg/BMI unit safe and no association between bleeding risk and anti-Xa level.[22]

As regards dalteparin, Leeman et al included 3,319 bariatric patients with a mean BMI of 43.3 kg/m^2.[23] They were administered 5,000 IU once daily during hospitalization only or for 14 days. Only two VTEs were found, both in the extended treatment group. Magee et al followed up 735 patients for 6 months and found no VTEs with dalteparin 5,000 IU once daily for 7 days.[24] Simoneau et al evaluated the biochemical efficacy of dalteparin 7,500 IE once daily and found that patients $>$ 180 kg reached only subtherapeutic anti-Xa levels.[25] In comparison, a small prospective study utilizing dalteparin 5,000 IU twice daily for 14 days found that $>$ 50% of patients (mean BMI, 43 kg/m^2) reached only subtherapeutic anti-Xa levels, but no VTEs were diagnosed during a 3-month follow-up.[26]

A single, large study on tinzaparin retrospectively included 1,212 bariatric patients with a median BMI of 47.9 - kg/m^2.[27] Low bleeding and VTE rates were observed with weight-based dosing of 75 IU/kg, and anti-Xa measurements showed no signs of accumulation. Notably, the utilized dose was higher than the recommended according to the product information (50 IU/kg).

All of the above-mentioned studies on patients undergoing bariatric surgery reported a low VTE rate. As a consequence, a likely associated floor effect impedes a credible comparison of the thromboprophylactic potential of the different dosing regimens. Also, the quality of the studies was limited since only one RCT was identified. Reassuringly, however, no safety issues were noted with any of the doses in question.

Nevertheless, a single, retrospective study did observe differences in thromboembolic event rates, namely, between patients receiving 30 mg twice daily and 40 mg twice daily, and this finding may suggest that the former dose is too low.[17] Also, the studies that included anti-Xa assessment did suggest that the standard fixed-dose of 40-mg enoxaparin or 5,000-IE dalteparin may be insufficient with increasing body weight. Therefore, a higher prophylactic dose may be considered in morbidly obese patients with BMI $\geq$ 40 kg/m^2. The European Society of Anaesthesiology reached a similar conclusion in their 2018 guideline on perioperative VTE prophylaxis in obese patients.[28] Here, it was recommended that the standard once daily prophylactic LMWH dose should be increased to 3 to 4,000 anti-Xa IU twice daily for obese patients with low risk of VTE and 4 to 6,000 anti-Xa IU twice daily for patients with high risk of VTE. Essentially, these recommendations imply that the standard fixed dose is to be administered twice daily instead of once daily. The evidence cited in the European Society of Anaesthesiology guideline to support these recommendations was, however, rather weak.

Lastly, most of the identified studies used in-hospital prophylaxis only, but in a few studies, LMWH was administered for an extended period of time after discharge, typically 10 days. Such strategy was found to be effective and safe and may be considered in high-risk patients (e.g., previous VTE, strong family history of VTE, and severe thrombophilia). A similar conclusion was reached by the European Society of Anaesthesiology.[28]

Prophylaxis in Nonbariatric Surgery

Two small studies investigating thromboprophylaxis with LMWH following nonbariatric surgery were identified (►**Table 2**). Al Otaib et al prospectively evaluated enoxaparin 0.5 mg/kg once daily in 50 patients with a mean BMI of 40.5 kg/m^2.[29] This approach was associated with satisfactory anti-Xa levels and low rates of VTE and bleeding. In comparison, Ludwig et al retrospectively evaluated enoxaparin 0.5 - mg/kg twice daily in 23 morbidly obese surgical intensive care patients and reached similar conclusions.[30]

Based on these results, a weight-based enoxaparin dosing regimen of 0.5 mg/kg may be appropriate in obese patients, but the few identified studies were too small to draw firm conclusions.

Prophylaxis in Medical or Trauma Inpatients

Out of six studies identified (►**Table 2**), a single RCT evaluated enoxaparin for medical inpatients. Four cohort studies prospectively evaluated enoxaparin as thromboprophylaxis for medical inpatients or trauma patients, whereas one study evaluated the pharmacodynamic properties of tinzaparin in healthy volunteers. No studies on dalteparin were identified under this category.

Miranda et al performed an RCT on 91 medical inpatients with a mean BMI of 37.8 kg/m^2, and enoxaparin 40 mg once daily was compared with 60 mg once daily.[31] No VTE events and a single major bleeding (in the 40-mg group) were observed. However, a significantly higher proportion (69 vs. 31%) reached target anti-Xa levels with 60 mg.

Rostas et al concluded in a prospective study that enoxaparin 30 mg twice daily was insufficient for the majority regardless of BMI based on biochemical evidence in a population with a mean BMI of 32.3 kg/m^2.[32] Another three prospective studies evaluated a weight-based dose of 0.5 - mg/kg once or twice daily in medical or trauma inpatients with mean BMI of 35 to 62 kg/m^2.[33–35] They all reached the same conclusion that such a weight-based dosing regimen was appropriate as regards clinical and biochemical efficacy, as well as safety, but the follow-up time was rather short ($<$ 10 days).

As for surgical thromboprophylaxis, it therefore seems that a fixed enoxaparin dose of 40 mg may be too low in obese patients, and several authors successfully utilized a weight-based dose of 0.5 mg/kg. Importantly, this recommendation primarily relies on biochemical evidence.

A prophylactic tinzaparin dose of 75 IU/kg was pharmacodynamically investigated by Hainer et al.[36] They reported

that the area under the curve for plasma anti-Xa was higher in obese patients, but otherwise, the weight-based dosage did not affect the pharmacokinetic parameters significantly in a comparison of obese and nonobese patients. Notably, the utilized dose was higher than the recommended according to the product information (50 IU/kg).

No eligible studies on dalteparin were identified. Notwithstanding, a post hoc analysis of a large RCT on dalteparin for thromboprophylaxis in medical inpatients (the PREVENT trial) has been published,[37] but was not included in the present review since it did not fulfill our eligibility criteria (obesity defined as BMI $\geq$ 28.6 kg/m^2 for women and $\geq$ 30 kg/m^2 for men). The study included 1,118 obese patients (median BMI, 32.9 kg/m^2), who were randomized to dalteparin 5,000 IU once daily or placebo. Dalteparin did not significantly reduce the event rate of the primary clinical endpoint in the obese subgroup by day 21 (VTE or death; relative risk [RR] = 0.64, 95% confidence interval [CI]: 0.32–1.28), but a BMI-stratified analysis did show a significant effect of dalteparin in the subgroup of patients with BMI of 30 to 34.9 kg/m^2. Importantly, the 3.3% of obese patients with BMI $\geq$ 40 kg/m^2 had a RR of approximately 1.0 versus placebo. Consequently, a dalteparin dose of 5,000 IE once daily may be considered insufficient in morbidly obese patients.

Low-Molecular-Weight Heparin Used for Treatment

For treatment, the recommended dose of enoxaparin is 1.0 mg/kg twice daily or 1.5 mg/kg once daily.[5] For tinzaparin, 175 IU/kg once daily is recommended,[6] and for dalteparin, 200 IU/kg once daily is recommended.[7] For dalteparin only, dose capping is advised with a maximum dose of 18,000 IU daily.[7]

LMWH in treatment doses was the topic of 18 of the identified studies (►**Table 3**). Most of these studies (15) were on enoxaparin: three RCTs, two prospective cohort studies, nine retrospective cohort studies based on medical chart review, and a single pharmacodynamic study. We identified one retrospective study on dalteparin and two pharmacodynamic studies on tinzaparin.

A post hoc analysis of two RCTs on enoxaparin versus UFH in patients with acute coronary syndrome investigated the effect of enoxaparin 1 mg/kg twice daily without dose capping.[38] The study included 1,839 patients with a BMI $\geq$ 30 kg/m^2 (mean BMI, 33.9 kg/m^2). Unfortunately, the proportion of morbidly obese patients (BMI $\geq$ 40 kg/m^2) was not specified. Obesity did not affect clinical outcomes in these trials in comparison with UFH, although a higher rate of nonmajor bleeding was observed in obese than in nonobese patients. In another RCT, Curry et al compared standard weight-based enoxaparin 1 mg/kg twice daily with a reduced dose of 0.8 mg/kg twice daily in morbidly obese patients (median BMI, 46.7 kg/m^2).[39] Similar proportions of patients reached anti-Xa target range, but fewer patients were above the target with reduced dose. Finally, Barras et al found no difference between enoxaparin dosed according to actual body weight or lean body weight for biochemical efficacy in a very small RCT with 11 obese patients.[40]

Two studies prospectively evaluated the biochemical efficacy of enoxaparin. Thompson-Moore et al found that morbidly obese patients (median BMI, 46.5 kg/m^2, $n = 41$) needed less than the recommended 1 mg/kg to avoid supratherapeutic anti-Xa levels,[41] whereas Bazinet et al concluded that no dose adjustment was required in patients with BMI $\geq$ 30 kg/m^2.[42] The majority of patients in the latter study had a BMI < 40 kg/m^2, and this circumstance may explain the apparent discrepancy.

Nine retrospective studies were identified in our search. Czupryn and Exline found that reducing the weight-based dose of enoxaparin to < 0.9 mg/kg in 462 obese patients (mean BMI, 44 kg/m^2) did not change the risk of thromboembolic events or bleedings during a short-term follow-up of 7 days.[43] Spinler et al focused on the safety of enoxaparin across different weight classes and found no difference in bleeding rates between standard dose and reduced dose (< 0.95 mg/kg) of enoxaparin in more than 1,000 patients weighing >120 kg.[44] Hagopian et al utilized standard dosage of enoxaparin capped at 150 mg and found no difference in clinical efficacy or safety in a comparison of patients with BMI below and above 40 kg/m^2 during 30-day follow-up.[45]

Six out of the nine retrospective studies primarily focused on the biochemical efficacy. Two studies reported that a reduced dose (median, 0.8 or 0.75 mg/kg, respectively) was sufficient to reach anti-Xa target in patients with BMI $\geq$ 40 kg/m^2 with a low incidence of bleedings and thromboembolic events.[46,47] Moreover, Lee et al conducted two studies in morbidly obese patients (BMI $\geq$ 40 kg/m^2) and concluded that the standard dose of 1 mg/kg was associated with a considerable risk of reaching supratherapeutic anti-Xa levels.[48,49] Also, Van Oosterom et al concluded that a dose of 0.75 to 0.85 mg/kg was most optimal in patients weighing > 100 kg based on anti-Xa levels.[50] On the contrary, Maclachlan et al found no difference in the proportion of patients reaching supratherapeutic anti-Xa levels with the recommended dose of 1 mg/kg twice daily in a comparison of patients weighing > 100 kg and patients weighing < 100 kg.[51] A relatively low rate of thromboembolic events and bleedings were observed in these studies, and generally, no effect of dose or obesity were observed for these outcomes.

A small pharmacodynamic study on enoxaparin was conducted by Sanderink et al.[52] The authors concluded that the standard dose of 1 mg/kg may be used in obese patients based on pharmacokinetics parameters, but the study only included a few patients with BMI > 40 kg/m^2.

When it comes to dalteparin, Al-Yaseen et al retrospectively evaluated the clinical efficacy and safety of a weight-adjusted dose without dose capping for the initial treatment of VTE before initiation of warfarin.[53] No VTE or bleeding events were observed in 153 patients weighing > 120 kg.

For tinzaparin, two pharmacodynamic studies were identified. Hainer et al included 137 volunteers with a mean weight of 129.6 kg, and Barrett et al included 30 patients with BMI > 30 kg/m^2.[36,54] Both studies concluded that a weight-based dose may be used without dose capping.

In conclusion, evidence from RCTs, prospective studies and retrospective studies on enoxaparin collectively

Table 3 Studies evaluating low-molecular-weight heparin for treatment in obese patients

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication and daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
Enoxaparin ($n = 15$)					
Randomized controlled trials					
2010, Barras et al[40]	RCT $\geq$ 100 kg, $n = 11$ Follow-up: 5 d Any indication	Individualized: enoxaparin, 1.5 mg/kg twice daily based on LBW vs. Conventional: enoxaparin 1.0 mg/kg twice daily or 1.5 mg/kg once daily (selected by prescriber)	Clinical efficacy NR Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL Safety NR	Biochemical efficacy Individualized vs. conventional: Time within range: 65.4 vs. 58.2%, $p = 0.27$ Time supratherapeutic: 10.4 vs. 0%, $p = 0.44$. Time subtherapeutic: 12.2 vs. 24.0%, $p = 0.46$	Individualized dosage of enoxaparin based on lean body weight was equally efficient as conventional dosage in obese individuals
2019, Curry et al[39]	RCT BMI $\geq$ 40 (median BMI: 46.7), $n = 54$ Follow-up: until anti-Xa in target range Any indication	Standard, enoxaparin, 1 mg/kg twice daily vs. reduced enoxaparin, 0.8 mg/kg twice daily	Clinical efficacy Recurrent VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.5–1.1 IU/mL) and time to reach target. Safety Major and minor bleeding	Clinical efficacy No thrombotic events Biochemical efficacy Standard vs. reduced; Within range: 76.9 vs. 89.3%, $p = 0.29$ Supratherapeutic: 6 cases vs. 1 case Subtherapeutic: 0 cases vs. 2 cases. Time to anti-Xa range: 31.9 vs. 28.6 h, $p = 0.7$ Safety No events	Reduced dose enoxaparin may be a reasonable dosing strategy in morbidly obese patients
2003, Spinler et al[38]	Post-hoc analysis of ESSENCE and TIMI 11B trials (RCTs) BMI $\geq$ 30 (mean = 33.9), $n = 1{,}839$ BMI < 30, $n = 5158$ Follow-up: 43 d Non-STEMI acute coronary syndrome	Enoxaparin, 1 mg/kg twice daily (preceded by 30 mg IV bolus in TIMI 11b trial), $n = 921$ vs. UFH, $n = 918$	Clinical efficacy Death, myocardial infarction (MI), urgent revascularization (UR) Biochemical efficacy NR Safety Major bleeding and hemorrhage	Clinical efficacy Obese UFH vs. enoxaparin; death, MI, UR: 18 vs. 14.3%, OR = 0.78 (95% CI: 0.61–1.0), $p = 0.05$ Obese vs. nonobese; 43-d mortality: 2.6 vs. 4.0%, $p = 0.09$ Safety Obese UFH vs. enoxaparin Major hemorrhage: 1.2 vs. 0.4%, OR = 0.38 (95% CI: 0.11–1.14),	Enoxaparin reduced the rate of the combined end point of death/MI/UR in the subgroups of patients who were obese and patients who were not obese. Obesity did not impact clinical outcomes in the combined analysis of ESSENCE and TIMI 11B

(*Continued*)

Table 3 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication and daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
				$p = 0.08$ Any hemorrhage: 5.3 vs. 11.7%, OR = 2.42 (95% CI: 1.69–3.45), $p < 0.001$ Obese vs. nonobese; Major hemorrhage: 0.8 vs. 1.3%, $p = 0.12$ Any hemorrhage: 8.5 vs. 6.8%, $p = 0.004$	
Prospective cohort studies					
2005, Bazinet et al[42]	Prospective cohort study BMI $\geq$ 30, $n = 81$ BMI = 18–30, $n = 131$ Follow-up: 5 d Any indication	Enoxaparin, 1.5 mg/kg once daily (obese, $n = 30$; controls, $n = 62$) or enoxaparin, 1 mg/kg twice daily (obese, $n = 51$; controls, $n = 69$)	Biochemical efficacy Anti-Xa (peak, steady state). Range: 1.0–2.0 IU/mL (once daily) or 0.5–1.1 IU/mL (twice daily) Safety NR	Biochemical efficacy 1.5 vs. 1 mg/kg Obese: Within range: 60 vs. 45% Supratherapeutic: 3 vs. 53% Subtherapeutic: 37 vs. 2% Controls: Within range: 58 vs. 46% Supratherapeutic: 2 vs. 51% Subtherapeutic: 40 vs. 3%	Based on anti-Xa, no dosage adjustments are required in obese patients
2015, Thompson-Moore et al[41]	Prospective cohort study BMI $\geq$ 40 or $\geq$ 140 kg (median BMI = 45.6), $n = 41$ Follow-up, median: 5 d Any indication	Recommended, enoxaparin 1 mg/kg ($\geq$ 0.95 mg/kg), $n = 18$ or reduced, enoxaparin0.95 mg/kg, $n = 23$	Clinical efficacy Thrombotic events Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.6–1.0 IU/mL Safety Bleeding	Clinical efficacy No events Biochemical efficacy Recommended vs. reduced; Within range: 23.5 vs. 52.6%, p = 0.07 Supratherapeutic: 70.6 vs. 31.6%, $p = 0.02$. Subtherapeutic: 5.9 vs. 15.8%, $p = 0.35$ Safety Recommended vs. reduced, bleeding: 22.2 vs. 17.9%, $p = 0.71$	Patients with morbid obesity required less than the recommended 1 mg/kg enoxaparin dose to achieve therapeutic peak anti-Xa levels
Retrospective cohort studies (chart reviews)					
2018, Czupryn and Exline[43]	Retrospective cohort study (chart review) 120 kg (median	Enoxaparin (< 90% of FDA-approved dose), $n = 56$ or enoxaparin ($\geq$	Clinical efficacy Ischemic stroke, VTE and death Biochemical	Clinical efficacy < 90 vs. $\geq$ 90%; VTE events: 0.0 vs. 0.74%, $p = 0.52$.	Reducing the dose of enoxaparin did not reduce the odds of major

Table 3 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication and daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	BMI 44.0), $n = 462$ Follow-up: 7 d from discharge Any indication	90% of FDA-approved dose), $n = 406$	efficacy NR Safety Major and minor bleeding	Ischemic stroke: 0.0 vs. 0.49%, $p = 0.60$ Safety < 90 vs. 90%; Major bleeding: 5.4 vs. 2.0%, $p = 0.12$ Minor bleeding events: 0.0 vs. 1.7%, $p = 0.32$ ≥ 150 kg vs. $\geq$ 120–150 kg: No difference in any outcome	bleeding or increase the odds of ischemic stroke or VTE
2011, Deal et al[46]	Retrospective cohort study (chart review) BMI ≥ 40 (median BMI = 49.5), $n = 26$. Follow-up, median: 6 d Any indication	Enoxaparin, weight-based, variable doses (median 0.8 mg/kg twice daily; range 0.5–1 mg/kg twice daily)	Clinical efficacy Recurrent VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.5–1 IU/mL Safety Bleeding	Clinical efficacy No events Biochemical efficacy Within range: 46% Supratherapeutic: 38% Subtherapeutic: 0% Uninterpretable: 15% Range reached: > 150 kg vs. < 150 kg: 46.7 vs. 45.5%, NS. Safety Total: 6 bleeding events. Supratherapeutic: 4 events (40%), $p = 0.033$	The majority in this cohort with morbid obesity achieved anti-Xa levels at or above goal at doses less than the recommended 1 mg/kg twice daily. Bleeding events were more frequent among patients with anti-Xa levels above goal
2013, Hagopian et al[45]	Retrospective cohort study (chart review) BMI ≥ 40, $n = 100$ BMI < 40, $n = 200$ Follow-up: 30 d Any indication	Enoxaparin, $\geq$ 0.85 mg/kg twice daily, dose capped at 150 mg Mean doses mg/kg: obese (0.96), controls (1.04)	Clinical efficacy Recurrent VTE Biochemical efficacy NR Safety Bleeding events up to 24 h after discontinuation	Clinical efficacy VTE: Obese vs. nonobese: 2 vs. 7 events, $p = 0.72$ Safety Bleeding events: Obese vs. nonobese: 29 vs. 23.5%, $p = 0.30$ Obese vs. normalweight, $p = 0.43$	Dosing enoxaparin in morbidly obese patients (up to 175 kg in weight) with doses capped at 150 mg was not associated with increased bleeding incidence
2015, Lalama et al[47]	Retrospective cohort study (chart review) BMI ≥ 40 (median BMI = 46.2), $n = 31$ Follow-up: 90 d Any indication	Enoxaparin 0.75 mg/kg twice daily	Clinical efficacy Recurrent VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.6–1.0 IU/mL Safety Bleeding	Clinical efficacy 1 VTE Biochemical efficacy Within range: 48% Supratherapeutic: 36% Subtherapeutic: 5% Safety 2 minor bleedings	Using a reduced enoxaparin dose of 0.75 mg/kg per dose in morbidly obese patients was likely to result in a therapeutic anti-Xa level without an increased risk for bleeding or thrombotic events

(*Continued*)

Table 3 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication and daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
2015, Lee et al[49]	Retrospective cohort study (chart review) BMI $\geq$ 40 or > 150 kg (mean BMI = 50.6), $n = 99$ Follow-up: not stated VTE, AF, acute coronary syndrome	Enoxaparin 1 mg/kg twice daily	Clinical efficacy NR Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.5–1.1 IU/mL Safety Bleeding	Biochemical efficacy Within range: 50.5% Supratherapeutic: 35.4% Subtherapeutic: 14.1% Safety No events	The majority was within target with standard dosing. Monitoring anti-Xa is warranted to avoid over-dosing in the obese patient population
2019, Lee et al[48]	Retrospective cohort study (chart review) BMI > 40–50, $n = 169$. BMI > 50–60, $n = 52$ BMI > 60, $n = 20$. Any indication	Enoxaparin, 1 mg/kg twice daily (initial median dose)	Clinical efficacy Thromboembolic events Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL Safety Bleeding	Clinical efficacy 1 thromboembolic event caused by HIT. Biochemical efficacy Within range BMI > 40–50; 38% BMI > 50–60; 35% BMI > 60–35% Supratherapeutic: BMI > 40–50; 53% BMI > 50–60; 62% BMI > 60; 65% Safety Major bleeding: 4.1% (all in BMI = 40–50 group)	Standard dosing of enoxaparin in morbidly obese patients will most likely lead to supratherapeutic anti-Xa levels, and a dose of 0.70 mg/kg is sufficient to reach therapeutic anti-Xa level in patients with BMI > 50
2019, Maclachlan et al[51]	Retrospective cohort study (chart review) > 100 kg (median BMI = 45.0), $n = 102$ < 100 kg, $n = 64$. Follow-up: 7–30 d Acute VTE	Enoxaparin 1 mg/kg twice daily	Clinical efficacy Recurrent VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL. Safety Major and CRNM within 30 d	Clinical efficacy Obese vs. normal weight: 0 vs. 4%, $p = 0.13$ Biochemical efficacy Obese vs. normal weight; Within range: 56 vs. 44%, $p = 0.15$. Supratherapeutic: 40 vs. 45%, $p = 0.99$. Subtherapeutic: 4 vs. 11%, $p = 0.11$ Safety Obese vs. normal weight; Major bleeding: 0 vs. 11%, $p = 0.003$ (within 30 d) CRNM, within 30 d: 4 vs. 5%, $p = 0.99$	These data support weight-based dosing of enoxaparin in obesity with no maximum dose
2009, Spinler et al[44]	Retrospective cohort study (chart	Enoxaparin, recommended dose:	Clinical efficacy NR	Safety Recommended vs.	Bleeding tended to be lower among

Table 3 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication and daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	review) ≤ 100 kg (mean BMI = 27.0), *n* = 15,162 101–120 kg (mean BMI = 34.6), *n* = 2,730 121–150 kg (mean BMI = 40.9), *n* = 994 > 150 kg (mean BMI = 53.7), *n* = 175 Non-STEMI acute coronary syndrome	0.95–1.05 mg/kg or enoxaparin, reduced dose: <0.95 mg/kg	Biochemical efficacy NR Safety Major bleeding and any intracranial hemorrhage	reduced dose; Bleeding risk: 100 kg: OR = 0.78 (95% CI: 0.69–0.89) 101–120: OR = 0.68 (0.48–0.95) 121–150 kg: OR = 0.99 (0.57–1.70) > 150 kg: OR = 2.42 (0.70–8.370)	patient groups weighing 120 kg or less when receiving recommended doses rather than reduced doses. No difference among patients >120 kg
2019, Van Oosterom et al[50]	Retrospective cohort study (chart review) > 100 kg (mean = 128 kg), *n* = 133 Follow-up: 30 d Specific indications NR	Enoxaparin < 0.75 mg/kg twice daily or enoxaparin 0.75–0.85 mg/kg twice daily or enoxaparin >0.85 mg/kg twice daily	Clinical efficacy Recurrent VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL. Safety Bleeding	Clinical efficacy 2 recurrent VTEs (PE); both with 1 mg/kg twice daily. Biochemical efficacy < 0.75 mg/kg vs. 0.75–0.85 vs. > 0.85 mg/kg; Within range: 62.29 vs. 62.1 vs. 58.2%. Supratherapeutic: 10.1 vs. 24.1 vs. 34.1% Subtherapeutic: 27 vs. 13.8 vs. 8.9% Safety 2 bleeding episodes: both supratherapeutic anti-Xa.	Dosing between 0.75–0.85 mg/kg appears to be a "safe" starting dose-range, however all obese patients should have anti-Xa monitoring due to high inter-patient variability
Pharmacodynamic studies					
2002, Sanderink et al[52]	Pharmacodynamic study Healthy volunteers, BMI ≥ 30 (mean BMI = 34.8), *n* = 24 BMI 18–25, *n* = 24 Follow-up: 7–9 d from last dose	Single dose subcutaneous enoxaparin, 1.5 mg/kg once daily for 4 consecutive days or a single 6 h intravenous infusion, 1.5 mg/kg enoxaparin	Clinical efficacy NR Biochemical efficacy Anti-Xa: Amax and AUC Anti-IIa: AUC Safety Death, major bleeding	Biochemical efficacy Obese vs. nonobese Anti-Xa, Amax: NS Anti-Xa AUC: Day 1: 14% higher in obese ($p = 0.006$) Day 4: 19% higher ($p = 0.002$) Anti-IIA, AUC: NS Safety No serious events	Enoxaparin was well tolerated when administered subcutaneously or intravenously, and there appears to be no need to modify the currently recommended dose for obese volunteers with BMI up to 40
Dalteparin (*n* = 1)					
2005, Al-Yaseen et al[53]	Retrospective cohort study (chart	Dalteparin, 200 IU/kg once daily	Clinical efficacy Recurrent VTE	Clinical efficacy Recurrent VTE: 3	It is safe to administer

(*Continued*)

Table 3 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication and daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	review) Total, $n = 193$ < 100, $n = 40$ 100–119 kg, $n = 93$ 120–139 kg, $n = 41$ > 140 kg, $n = 19$ Follow-up: 90 d VTE	for 5–7 d ($n = 98$) (followed by VKA) or dalteparin, 100 IU/kg twice daily for 5–7 d ($n = 55$) (followed by VKA)	Biochemical efficacy NR Safety Bleeding	(1.6%; after change to VKA). Safety Major bleedings: 2 (1.0%; after change to VKA)	dalteparin at or near full dose based on actual body weight for the treatment of acute venous thromboembolism without an increased risk of major hemorrhage
Tinzaparin ($n = 2$)					
2001, Barrett et al[54]	Pharmacodynamic study BMI < 30, $n = 157$ BMI ≥ 30, $n = 30$ Follow-up: NR Proximal DVT	Tinzaparin 175 IU/kg once daily	Clinical efficacy NR Biochemical efficacy Plasma anti-Xa (pharmacodynamic model). Safety NR	Biochemical efficacy Body weight was not a significant covariate in the model. Clearance in obese patients decreased by 22%	The effect of obesity is probably not clinically significant, and no dose capping should be applied
2002, Hainer et al[36]	Pharmacodynamic study Volunteers, 101–-165 kg (mean, 129.6 kg), $n = 37$ Control subjects < 100 kg from prior studies, $n = 27$. Follow-up: 8 d from second dose	Single dose tinzaparin 175 IU/kg (prophylactic dose, see ►**Table 2**)	Clinical efficacy NR Biochemical efficacy Anti-Xa: Amax (-IU/mL), AUC (IU*-h/mL) Anti-IIa: Amax(-IU/mL), AUC (IU*-h/mL) Safety Bleeding events	Biochemical efficacy Obese vs. controls Anti-Xa; AUC: 9.99 (95% CI: 9.336–-10.652) vs. 9.55 (8.961–10.139) Amax: 0.81 (95% CI: 0.759–0.859) vs. 0.87 (0.784–0.956) Anti-IIa; AUC: 4.34 (95% CI: 3.926–4.760) vs. 3.53 (3.278–3.782) Amax: 0.34 (95% CI: 0.307–0.373) vs. 0.33 (0.304–0.356) Safety No major bleeding events	SC tinzaparin dosing in heavy or obese patients is appropriate based on body weight alone; the dose need not be capped at a maximal absolute dose

Abbreviations: AUC, area under the activity-time curve; Amax, observed maximal activity; BMI, body mass index (kg/m^2); CI, confidence interval; CRNM, clinically relevant non-major bleeding; LBW, lean body weight; NR, not reported; NS, non-significant; OR, odds ratio; PE, pulmonary embolism; TBW, total body weight; VTE, venous thromboembolism.

suggests that supratherapeutic anti-Xa levels are more likely to be reached when the standard dose of 1 mg/kg twice daily is administered to patients with a BMI ≥ 40 kg/m^2. On the other hand, for lower BMI classes, no such phenomenon is observed. Consequently, a reduced weight-based dose of approximately 0.8 mg/kg twice daily may be considered in morbidly obese patients. The clinical implications, however, remain uncertain, since we found no evidence that standard dosage was associated with an increased risk of bleeding.

Another review on the topic by McCaughan et al concluded that no firm recommendations could be made in patients with a BMI ≥ 40 kg/m^2 due to limited evidence.[55] However, in the present study, we did identify several additional, recently published studies, which support our conclusion.

Table 4 Studies evaluating non–vitamin K antagonist oral anticoagulants for thromboprophylaxis in obese patients ($n = 4$)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
Randomized controlled trials					
2012, Eriksson et al[56]	Post hoc analysis of RE-MODEL, RE-NOVATE, RE-NOVATE II (RCTs) BMI > 20–25, $n = 1,417$ BMI > 25–30, $n = 2,373$ BMI > 30, $n = 1,826$ Follow-up: 3 mo Thromboprophylaxis (orthopedic surgery)	Dabigatran, 220 mg once daily ($n = 2,835$) vs. enoxaparin, 40 mg once daily ($n = 2,851$)	Clinical efficacy Major VTE and VTE-related mortality Biochemical efficacy NR Safety Major, clinically relevant or any bleeding	Clinical efficacy Dabigatran vs. enoxaparin, event rate with OR (95% CI): BMI > 30; 2.7 vs. 2.9%, OR = 0.92 (0.49–1.74), $p = 0.797$ BMI > 20–25; 2.1 vs. 4.3%, OR = 0.48 (0.24–0.97), $p = 0.037$. No correlation between major VTE rates and BMI found. Safety Dabigatran vs. enoxaparin, BMI > 30, event rate with OR (95% CI): major bleedings: 1.3 vs. 1.1%, OR = 1.25 (0.54–2.91) Major or clinically relevant bleedings: 5.4 vs. 4.6%, OR = 1.17 (0.77–1.78) Any bleeding: 12.4 vs. 12.0%, OR = 1.03 (0.78–1.37)	Dabigatran and enoxaparin were equally effective in protection against VTE and bleeding among obese and no correlation between VTE-rates and BMI found
2013, Pineo et al[57]	Post hoc analysis of ADVANCE studies (2 RCTs) BMI < 25, $n = 2,006$ BMI 25–29, $n = 3,368$ BMI ≥ 30, $n = 3,065$ Follow-up: 14–38 d Thromboprophylaxis after knee or hip arthroplasty	Apixaban, 2.5 mg once daily, $n = 4,236$ vs. enoxaparin, 40 mg once daily, $n = 4,228$	Clinical efficacy VTE Biochemical efficacy NR Safety Major bleeding, CRNM bleeding	Clinical efficacy Total events: 74 Apixaban vs. enoxaparin BMI-effect, interaction $p = 0.2273$ Safety Major bleedings: 63 CRNM bleedings: 388. Apixaban vs. enoxaparin BMI-effect, interaction	No evidence found that BMI influences the balance of benefit to risk for apixaban compared with enoxaparin

(*Continued*)

Table 4 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
				$p = 0.5082$ (major bleeding), $p = 0.3223$ (CRNM bleeding)	
Retrospective cohort studies (chart reviews)					
2019, Krauss et al[58]	Retrospective cohort study (chart review) BMI ≥ 30, $n = 687$ BMI < 30, $n = 554$ Follow-up: 35 d Thromboprophylaxis after total joint arthroplasty	Rivaroxaban, 10 mg once daily	Clinical efficacy VTE Biochemical efficacy NR Safety Bleeding	Clinical efficacy Similar number of VTE events in normal weight and obese patients (0.4%). Safety Major bleedings in 6.1% normal weight vs. 5.0% obese ($p = 0.36$)	The fixed-dose rivaroxaban as thromboprophylaxis is not associated with an increased risk of major bleeding or VTE in patients with a high bodyweight
Pharmacodynamic studies					
2007, Kubitza et al[59]	Pharmacodynamic study (randomized) Rivaroxaban: 70–80 kg, $n = 12$ > 120 kg, $n = 12$ Placebo, all weights, $n = 12$ Healthy volunteers	Rivaroxaban 10 mg (single dose) vs. placebo	Clinical efficacy Not reported Biochemical efficacy Pharmacodynamics and pharmacokinetics Safety Adverse events	Biochemical efficacy No difference in AUC plasma concentration, Cmax or half-life. Safety 6 events (3 patients) in 70–80 kg group; 6 events (4 patients) in > 120 kg group; 0 events in placebo group	Rivaroxaban is unlikely to require dose adjustment for body weight

Abbreviations: AUC, area under the concentration-time curve; BMI, body mass index (kg/m^2); CI, confidence interval; Cmax, maximum plasma concentration; CRNM, clinically relevant non-major bleeding; NR, not reported; NS, non-significant; OR, odds ratio; PE, pulmonary embolism; RCT, randomized, controlled trial; VTE, venous thromboembolism.

For dalteparin and tinzaparin, only a few studies were identified, and the number of included morbidly obese patients was low. However, the studies did indicate that no dose capping seems to be necessary in patients weighing < 140 kg.

Non–Vitamin K Antagonist Oral Anticoagulants Used for Prophylaxis

Four studies on NOAC as thromboprophylaxis were identified (►**Table 4**). Two studies were post hoc analyses of RCTs on dabigatran and apixaban, respectively, for thromboprophylaxis following orthopedic surgery, whereas one study retrospectively assessed rivaroxaban for thromboprophylaxis following joint arthroplasty. The fourth study was a pharmacokinetic study on rivaroxaban involving healthy volunteers.

The two post hoc analyses of RCTs did not find impaired safety or clinical efficacy of apixaban 2.5 mg once daily or dabigatran 220 mg once daily in obese patients (BMI $\geq$ 30 - kg/m^2) in comparison with enoxaparin 40 mg once daily.[56,57] However, the number of morbidly obese patients was not specified in the apixaban study, and only 2% of the patients in the dabigatran study had a BMI $\geq$ 40 kg/m^2. Consequently, none of them included a separate subgroup analysis on morbidly obese patients.

The single retrospective study on rivaroxaban 10 mg once daily did not show differences in VTE or bleeding rates between nonobese and obese patients (BMI $\geq$ 30 kg/m^2), but no data on the subgroup of patients with BMI $\geq$ 40 kg/m^2 was available.[58] Finally, the pharmacokinetic study by Kubitza et al found similar peak levels and area under the curve for plasma rivaroxaban levels in healthy volunteers weighing 70 to 80 kg, as well as > 120 kg.[59]

In conclusion, limited evidence is available for the use of NOAC as thromboprophylaxis in obese patients. In particular, none of the identified studies included a subgroup analysis on morbidly obese patients (BMI $\geq$ 40 kg/m^2).

Non–Vitamin K Antagonist Oral Anticoagulants Used for Treatment

Considerable uncertainty has existed about the effect of NOAC in obese individuals with AF or VTE, although the large phase-III trials did include several such patients.[60] Unfortunately, the data were analyzed in a dichotomized way (normal weight/obese) without stringent BMI stratification, and the weight cut-offs for obesity varied between the studies. Indeed, no studies reported the number of included morbidly obese patients (BMI $\geq$ 40 kg/m^2) or the outcome of this subgroup. Consequently, in 2016, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis cautioned against the use of NOAC in patients weighing > 120 kg or BMI > 40 kg/m^2.[60]

In the present review, 20 studies on NOAC used for treatment were identified (►**Table 5**). Seven studies were post hoc analyses based on data from the large phase-III RCTs on NOAC for patients with AF or VTE, and only one prospective study on NOAC for AF/VTE was identified. The clinical efficacy of NOAC as regards prevention of stroke/systemic embolism or VTE recurrence was retrospectively evaluated in nine studies. The remaining three studies mainly focused on pharmacokinetics or biochemical efficacy of NOAC in obese patients.

Several succeeding post hoc analyses on weight-stratified data from the NOAC phase-III RCTs have been published. For rivaroxaban, a BMI-stratified analysis showed that the clinical efficacy and safety were comparable with warfarin in patients with AF and VTE across BMI groups.[61,62] The highest BMI group comprised patients with BMI $\geq$ 35 kg/m^2, and rivaroxaban was even found superior to warfarin in AF patients with BMI $\geq$ 35 kg/m^2 for stroke prevention. Still, no separate analysis on patients with BMI $\geq$ 40 kg/m^2 was performed. The ENGAGE AF-TIMI trial on edoxaban for AF included 1,149 patients with a BMI $\geq$ 40 kg/m^2.[63] In the post hoc analysis, no interaction between the BMI groups and efficacy or safety was found, although a subanalysis limited to ischemic stroke did show statistically significantly higher risk in the edoxaban group (8/415) than in the warfarin group (2/364) among patients with BMI $\geq$ 40 kg/m^2 (hazard ratio = 4.32 [1.11–16.8]). In parallel, the ENSURE-AF trial of patients subjected to electrical cardioversion showed similar efficacy and safety of warfarin and edoxaban in patients with BMI $\geq$ 30 kg/m^2.[64] No weight-stratified post hoc analysis on edoxaban for VTE patients has been performed. A post hoc analysis of the ARISTOTLE trial on apixaban in AF patients included 1,006 patients with BMI $\geq$ 40 kg/m^2.[65] The effect relative to warfarin was not affected by BMI group. Interestingly, however, apixaban was associated with a lower bleeding risk than warfarin in nonobese patients only (BMI < 30 kg/m^2). In another post hoc analysis of the same ARISTOTLE trial, similar effect of apixaban and warfarin was again seen in all patients weighing > 120 kg.[66] Interestingly, the study included a subanalysis of 724 patients weighing between 121 and 140 kg, and in these patients, apixaban was even found to be more effective than warfarin. In the highest weight group (> 140 kg), too few patients were included to draw a firm conclusion.

When it comes to apixaban as treatment for VTE, no weight-stratified post hoc analysis was identified in our search. As regards dabigatran, no weight-stratified post hoc analyses were identified. However, Reilly et al investigated plasma dabigatran concentrations from the RE-LY trial (dabigatran for AF) and found that obese patients (> 100 kg) had 21% lower plasma dabigatran concentration.[67] Also, the risk of ischemic events was inversely correlated with plasma dabigatran concentration, but no BMI-stratified analysis of clinical efficacy was performed.

A single prospective registry study by Tittl et al on NOAC was found.[68] The majority of the included patients received rivaroxaban or apixaban (> 80%), and the main indication was AF (68%) followed by VTE (31%). The study included 3,432 patients of which 346 patients had BMI $\geq$ 35 kg/m^2 and 98 BMI $\geq$ 40 kg/m^2. The thromboembolic and bleeding event rates were found to be similar across BMI classes with a median follow-up time of 998 days.

We also identified nine retrospective studies that analyzed chart summaries of patients treated with NOAC.

Table 5 Studies evaluating non–vitamin K antagonist oral anticoagulants for treatment in obese patients ($n = 20$)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
Randomized controlled trials					
2017, Balla et al[61]	Post hoc analysis of ROCKET AF trial (RCT) BMI: 18.5–24.9, $n = 3,289$ BMI = 25–29.9, $n = 5,535$ BMI $\geq$ 30, $n = 5,206$ (including BMI 35–40, $n = 1,278$ and BMI $\geq$ 40, $n = 620$) Follow-up, median: 2 y AF	Rivaroxaban, 15–20 mg once daily vs. warfarin	Clinical efficacy Stroke or systemic embolism Biochemical efficacy NR Safety Major and CRNM events	Clinical efficacy Rivaroxaban vs. warfarin: BMI effect normal weight vs. overweight vs. obese, interaction: $p = 0.40$ BMI $\geq$ 35 vs. normal weight on rivaroxaban: HR = 0.62 (95% CI: 0.40–0.96, $p = 0.033$) Safety Rivaroxaban vs. warfarin: BMI effect normal weight vs. overweight vs. obese, interaction: $p = 0.01$ Normal weight: HR = 0.97 (95% CI: 0.84–1.13) BMI = 25–30: HR = 1.18 (1.05–1.33) BMI > 30; HR = 0.93 (0.82–1.04) No safety data reported on rivaroxaban for BMI > 35	Warfarin and rivaroxaban equally effective in all BMI groups, but lower risk of stroke in patients with BMI $\geq$ 35 vs. normal-weight on rivaroxaban. In overweight, but not obese or normal-weight, a higher risk of major or CRNM bleeding was observed with rivaroxaban
2019, Boriani et al[63]	Post hoc analysis of ENGAGE AF-TIMI 48 trial (RCT) BMI: < 18.5, $n = 177$ BMI = 18.5– < 25, $n = 4,491$ BMI = 25– < 30, $n = 7,903$ BMI = 30– < 35, $n = 5,209$ BMI = 35– < 40, $n = 2,099$ BMI $\geq$ 40, $n = 1,149$	Edoxaban high dose, 60 mg once daily vs. Edoxaban low dose, 30 mg once daily vs. warfarin	Clinical efficacy Stroke or SEE Biochemical efficacy Anti-Xa and plasma edoxaban levels (trough, steady state). Safety Events of major bleeding and major and CRNM	Clinical efficacy High dose edoxaban vs. warfarin: BMI group effect (interaction), $p = 0.16$ (continuous BMI interaction $p = 0.93$). Low-dose-edoxaban vs. warfarin: BMI group effect (interaction), $p = 0.063$ (continuous BMI interaction $p = 0.92$).	The effects of edoxaban vs. warfarin on stroke/SEE, major bleeding, and net clinical outcome were similar across BMI groups. Similarly, no difference in plasma edoxaban trough level across BMI groups. Significantly lower bleeding event rates with low-dose

Table 5 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	Follow-up, median: 2.8 y AF			Biochemical efficacy No association between BMI and plasma edoxaban/anti-Xa levels. Safety Edoxaban vs. warfarin: no BMI group effect for low or high dose edoxaban	edoxaban in all subgroups, and nonsignificant lower rates with high dose edoxaban
2016, Di Nisio et al[62]	Post hoc analysis of EINSTEIN trials (2 RCTs) BMI < 25, $n = 2{,}481$ BMI ≥ 25–30, $n = 3{,}258$ BMI ≥ 30–35, $n = 1{,}630$ BMI ≥ 35, $n = 861$ Follow-up: 3–12 mo VTE	Rivaroxaban, 15 mg twice daily for 21 d followed by 20 mg once daily vs. enoxaparin followed by VKA	Clinical efficacy Recurrent VTE Biochemical efficacy NR Safety Major bleeding and clinically relevant bleeding	Clinical efficacy No association between recurrent VTE and bodyweight ($p = 0.87$) or BMI ($p = 0.62$). HR for rivaroxaban vs. enoxaparin/VKA was similar in all bodyweight and BMI categories. Safety No association between major or clinically relevant bleedings and bodyweight ($p = 0.87$/$p = 0.17$) or BMI ($p = 0.36$/$p = 0.63$). HR for rivaroxaban vs. enoxaparin/VKA was similar in all bodyweight and BMI categories	The fixed-dose rivaroxaban regimen is not associated with an increased risk of major bleeding or recurrent VTE in patients with a high bodyweight
2019, Hohnloser et al[66]	Post hoc analysis of the ARISTOTLE trial (RCT) > 60–120 kg, $n = 15{,}172$ 121–140 kg, $n = 724$ > 140 kg, $n = 258$ Follow-up: 2 y AF	Apixaban, 2.5–5 mg twice daily vs. warfarin	Clinical efficacy Stroke/SEE; death; stroke/SEE/MI/Death Biochemical efficacy NR Safety Major bleeding	Clinical efficacy Apixaban vs. warfarin Stroke/SEE: 121–140 kg: HR = 0.21 (95% CI: 0.05–0.95) > 140 kg: HR = 2.35 (0.21–25.95) Death/MI: NS. Safety Apixaban vs. warfarin	Apixaban was at least equally effective and safe as warfarin in all weight groups. Apixaban may be superior to warfarin as regards efficacy and safety in obese patients 121–140 kg

(*Continued*)

Table 5 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
				Major bleeding: NS Major or CRNM bleeding: 121–140 kg: HR = 0.46 (95% CI: 0.26–0.84) > 140 kg: HR = 1.21 (0.42–3.46)	
2019, Lip et al[64]	Post hoc analysis of ENSURE-AF trial (RCT) BMI ≥ 30, *n* = 1,067 BMI < 30, *n* = 1,132 Follow-up: 58 d Patients undergoing cardioversion of AF	Edoxaban, 60 mg once daily (*n* = 1095) vs. enoxaparin-warfarin, (*n* = 1104)	Clinical efficacy Stroke, SEE, MI, and cardiovascular death Biochemical efficacy NR Safety Major and CRNM bleeding	Clinical efficacy Edoxaban vs. enoxaparin-warfarin, event rate: BMI ≥ 30: 0.8 vs. 0.9%, OR = 0.81 (0.16–3.78) BMI < 30: 0.2 vs. 1.1%, OR = 0.17 (95% CI: 0–1.37) Safety Edoxaban vs. enoxaparin-warfarin, event rate BMI ≥ 30: 1.6 vs. 1.1%, OR = 1.37 (0.41–4.82) BMI < 30: 1.5 vs. 0.9%, OR = 1.62 (0.46–6.34)	BMI did not significantly impact the relative efficacy and safety of edoxaban vs. enoxaparin-warfarin
2014, Reilly et al[67]	Post hoc analysis of the RE-LY trial (RCT) 50– < 100 kg, *n* = 6,852 ≥ 100 kg, *n* = 1,433 Follow-up: median 2.0 y AF	Dabigatran 110 mg twice daily vs. dabigatran 150 mg twice daily	Clinical efficacy NR Biochemical efficacy Plasma dabigatran concentration Safety NR	Biochemical efficacy Dose-normalized plasma concentration: 50–< 100 kg: 0.84 ng/mL/mg ≥ 100 kg: 0.66 ng/mL/mg	Obese had 21% lower plasma concentration compared with normal weight. Risk of ischemic events was inversely correlated with plasma concentration, whereas bleedings increased with drug exposure
2016, Sandhu et al[65]	Post hoc analysis of the ARISTOTLE trial (RCT) BMI = 18.5– < 25, *n* = 4,052 BMI = 25– < 30, *n* = 6,702 BMI = 30– < 35, *n* = 4,379	Apixaban, 2.5–5 mg twice daily (standard dosage) vs. warfarin	Clinical efficacy Stroke/SEE; death; stroke/SEE/MI/Death Biochemical efficacy NR Safety Major bleeding	Clinical efficacy Apixaban vs. warfarin, BMI effect: Stroke/SEE, interaction, *p* = 0.11 –Death, interaction *p* = 0.44 –Stroke/SEE/MI/death, interaction *p* = 0.20	Apixaban was equally effective as warfarin in all BMI groups. Apixaban was associated with a lower risk of major bleedings than warfarin only in patients with BMI < 30

Table 5 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	BMI = 35– < 40, $n = 1{,}775$ BMI ≥ 40, $n = 1{,}006$ Follow-up, median: 1.8 y AF			Safety Apixaban vs. warfarin, BMI effect: Major bleeding, $p = 0.04$ (lower bleeding risk with apixaban only with BMI < 30)	
Prospective cohort studies					
2018, Tittl et al[68]	Prospective cohort study (medical reports) BMI = 18.5–24.9, $n = 892$ BMI = 25–29.9, $n = 892$ BMI = 30–34.9, $n = 731$ BMI ≥ 35, $n = 346$ Follow-up: 998 d (mean) Any indication	Rivaroxaban (61.3%), apixaban (20.0%), dabigatran (10.1%) or edoxaban (8.6%) Standard dose (73.3%) or reduced dose (26.7%)	Clinical efficacy Combined effectiveness (stroke, TIA, SEE, VTE) Biochemical efficacy NR Safety Major bleeding	Clinical efficacy Over-all event rate, BMI < 30 vs. BMI ≥ 30: 4.3 vs. 3.7% Event rate/100 patient-years (95% CI): BMI = 30–35: 1.84 (1.24–2.63) BMI = 35–40: 1.56 (0.71–2.96) BMI > 40; 0.49 (0.01–2.71) Time to first event, $p = 0.1145$ between weight groups Safety Over-all event rate, BMI < 30 vs. BMI ≥ 30: 5.5 vs. 5.0% Event rate/100 patient-years: BMI = 30–35; 2.09 (1.44–2.91) BMI = 35–40; 2.23 (1.19–3.81) BMI > 40; 0.49 (1.39–7.12) Time to first bleeding, $p = 0.3316$ between weight groups	In a large set of real-life NOAC recipients, high BMI was not associated with inferior NOAC effectiveness or safety
Retrospective cohort studies (chart reviews)					
2019, Aloi et al[75]	Retrospective cohort study (chart review)		Clinical efficacy Recurrent VTE	Clinical efficacy VTE recurrence rate:	No difference in VTE recurrence in obese

(*Continued*)

Table 5 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	< 120 kg, $n = 1{,}063$ ≥ 120 kg, $n = 133$ Follow-up, mean: 212.2 d (<120 kg) vs. 241.6 d (≥ 120 kg) VTE	Apixaban, $n = 227$ Dabigatran, $n = 353$ Rivaroxaban, $n = 616$	Biochemical efficacy NR Safety NR	1.1% (< 120 kg) vs. 0.8% (≥ 120 kg), $p = 0.69$	patients ≥ 120 kg compared with patients <120 kg
2016, Arachchillage et al[76]	Retrospective cohort study (chart review) 50–120 kg, $n = 135$ > 120 kg (mean BMI 42.4), $n = 45$ Follow-up, median: 14 mo VTE	Rivaroxaban, 15 mg twice daily in 3 wk followed by 20 mg once daily	Clinical efficacyRecurrent VTE Biochemical efficacy Plasma rivaroxaban level (peak, steady state). Safety Major bleedings and clinically relevant events	Clinical efficacy No association between recurrent VTE and rivaroxaban levels or bodyweight Biochemical efficacy Mean rivaroxaban level: 50–120 vs. > 120 kg; 308 vs. 281 ng/mL, $p = 0.28$ Safety No association between bleeding and rivaroxaban levels or bodyweight	Similar plasma rivaroxaban levels in normal weight and obese patients. No association between clinical efficacy or safety outcomes and levels of rivaroxaban or weight
2019, Kalani et al[72]	Retrospective cohort study (chart review) BMI > 40 or weight > 120 kg (mean BMI = 46.3), $n = 180$ Follow-up: NR Any indication	Apixaban, $n = 46$ Dabigatran, $n = 11$ Rivaroxaban, $n = 33$ or warfarin, $n = 90$	Clinical efficacy Combined endpoint: stroke, TIA, DVT, PE, or MI. Biochemical efficacy NR Safety Major bleeding	Clinical efficacy Combined endpoint: DOAC: 11 events; warfarin: 10 events, OR = 1.11; 95% CI: 0.45–2.78; $p = 0.82$. Safety Major bleeding: 1 patient on rivaroxaban; 1 patient on apixaban	Anticoagulation therapy with DOACs in morbidly obese patients may be a safe and effective alternative to warfarin for prevention of stroke or systemic embolic events
2019, Kido and Ngorsuraches [73]	Retrospective cohort study (chart review) BMI > 40 or weight > 120 kg (mean BMI = 44.8), $n = 128$ Follow-up: 5.8 y AF or flutter	DOAC (dabigatran, $n = 20$; rivaroxaban, $n = 25$; apixaban, $n = 19$) or warfarin ($n = 64$)	Clinical efficacy Ischemic stroke or TIA Biochemical efficacy NR Safety Major bleeding.	Clinical efficacy Incidence rate: 1.75%/year (DOAC); 2.07%/year (warfarin); RR = 0.84 (95% CI: 0.23–3.14), $p = 0.80$. Adjusted OR: OR = 0.81 (95% CI: 0.20–3.27, $p = 0.77$ Safety	DOACs and warfarin were equally effective in obese with no significant difference in efficacy and safety outcomes

Table 5 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
				Major bleeding: DOAC vs. warfarin: RR 0.44 (95% CI: 0.15–1.25), $p = 0.11$	
2019, Kushnir et al[69]	Retrospective cohort study (chart review) BMI $\geq$ 40 (mean BMI 44.7), $n = 795$ Follow-up: 196 d (mean, VTE) or 359.4 d (mean, AF) VTE or AF	Apixaban, $n = 150$ (5 mg twice daily (89%); 2.5 twice daily (9%); 10 mg twice daily (<1%); 2.5–5 mg twice daily (2%) or rivaroxaban, $n = 326$ (20 mg once daily (94%); 15 mg once daily (4%); 15 mg twice daily (1%); 10 mg once daily (< 1%) vs. warfarin, $n = 319$	Clinical efficacy Incidence of recurrent VTE and stroke Biochemical efficacy NR Safety Major bleedings and any clinically relevant bleeding	Clinical efficacy Total events, $n = 6$ (VTE)/7 (AF) NOAC vs. warfarin: VTE, $p = 0.74$; stroke, $p = 0.71$ Safety Major bleeding: Total events, $n = 7$ (VTE)/20 (AF); NOAC vs. warfarin: $p = 0.77$ (VTE); $p = 0.063$ (AF in favor of NOAC) Clinically relevant bleedings NOAC vs. warfarin: $p = 0.45$ (VTE); $p = 0.16$ (AF)	Similar efficacy and safety between apixaban/rivaroxaban and warfarin in morbidly obese patients
2019, Netley et al[77]	Retrospective cohort study (chart review) BMI < 30, $n = 1,575$ BMI = 30–40, $n = 1,288$ BMI > 40, $n = 595$ Follow-up: NR Any indication	Rivaroxaban (47.8%), apixaban (42.0%), dabigatran (10.2%)	Clinical efficacy DVT, PE, arterial embolism Biochemical efficacy NR Safety Overt bleeding events	Clinical efficacy Total events, $n = 43$ No effect of BMI group ($p = 0.598$) Safety Total events, $n = 70$ No effect of BMI group ($p = 0.065$, in favor of high BMI)	Obesity did not correlate with thrombotic or overt bleeding complications
2019, Perales et al[74]	Retrospective cohort study (chart review) BMI > 40 or weight > 120 kg (mean BMI = 45.0), $n = 176$ Follow-up: 12 mo VTE or AF	Rivaroxaban, $n = 84$ or warfarin, $n = 92$	Clinical efficacy Composite endpoint: VTE recurrence, stroke incidence, or mortality. Biochemical efficacy NR Safety Bleeding	Clinical efficacy Composite endpoint: rivaroxaban (5%) vs. warfarin (13%), $p = 0.06$ Safety Bleeding: rivaroxaban (8%) vs. warfarin (2%), $p = 0.06$	Although not statistically significant, rivaroxaban strongly trended toward a lower incidence of clinical failure, but higher incidence of bleeding, in comparison with warfarin in morbidly obese patients

(*Continued*)

Table 5 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
2019, Peterson et al[70]	Retrospective cohort study (US healthcare claims database) BMI $\geq$ 40, $n = 7{,}126$ (3,563 matched pairs) Follow-up: mean 10.3 mo (rivaroxaban)/10.6 mo (warfarin) AF	Rivaroxaban, 20 mg once daily (81.4%), dose NR for the remaining or warfarin	Clinical efficacy Ischemic stroke or SEE Biochemical efficacy NR Safety Major bleeding	Clinical efficacy Event rate per person per year: 0.001 (rivaroxaban) vs. 0.002 (warfarin); $p = 0.3592$ Safety Event rate per person per year: 0.03 (rivaroxaban) vs. 0.03 (warfarin); $p = 0.2570$	Morbidly obese AF patients treated with rivaroxaban had comparable risk of ischemic stroke/systemic embolism and major bleeding as those treated with warfarin
2019, Spyropoulos et al[71]	Retrospective cohort study (US healthcare claims database) BMI $\geq$ 40, $n = 5{,}780$ (2,890 matched pairs) Follow-up, mean: 10.0 mo (rivaroxaban)/10.5 mo (warfarin) VTE	Rivaroxaban or warfarin	Clinical efficacy Recurrent VTE Biochemical efficacy NR Safety Major bleeding	Clinical efficacy Event rate per person per year: 0.24 (rivaroxaban) vs. 0.25 (warfarin); $p = 0.2234$ Safety Event rate per person per year: 0.34 (rivaroxaban) vs. 0.32 (warfarin); $p = 0.6370$	Morbidly obese VTE patients treated with rivaroxaban had comparable risk of recurrent VTE and major bleeding as those treated with warfarin
Pharmacodynamic studies					
2018, Piran et al[78]	Pharmacodynamic study BMI $\geq$ 40 or >120 kg (mean BMI = 41.0), $n = 38$ Follow-up: 4 mo Treatment, any indication	Apixaban ($n = 7$) Dabigatran ($n = 10$) Rivaroxaban ($n = 21$)	Clinical efficacy Stroke and VTE Biochemical efficacy Patients below expected median peak and trough drug concentrations Safety NR	Clinical efficacy No events Biochemical efficacy 2 patients (both on dabigatran) (5%) had a peak plasma concentration lower than median trough. 8 patients (2 dabigatran, 6 rivaroxaban) (21%) had a peak concentration below the fifth percentile (10th percentile for dabigatran)	The majority of obese were within usual on-treatment range and 21% were below
2013, Upreti et al[80]	Pharmacodynamic study > 120 kg or BMI $\geq$ 30 (mean BMI 42.6), $n = 19$ Reference group,	Apixaban, single dose, 10 mg	Clinical efficacy NR Biochemical efficacy Plasma anti-Xa (15 measurements over 72	Biochemical efficacy Plasma AUC and Cmax, respectively, 23 and 31% lower than reference group.	The modest change in apixaban exposure is unlikely to require dose adjustment based on body weight alone

Table 5 (*Continued*)

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
	65–85 kg, $n = 18$ Follow-up: 72 h Healthy volunteers		h) Safety Adverse effects	Safety Adverse effects: 12 (all mild or moderate, no bleeding)	
2019, Wasan et al[79]	Pharmacodynamic study $\leq$ 120 kg, $n = 23$ $>$ 120 kg (mean BMI = 49.0), $n = 23$ Follow-up: 4 h VTE, AF or peripheral arterial disease	Apixaban, 5 mg twice daily	Clinical efficacy NR Biochemical efficacy Anti-Xa (trough + peak (2 + 4 h) Safety NR	Biochemical efficacy Similar trough anti-Xa levels in patients $\leq$ 120 kg and $>$ 120 kg ($p = 0.4$). 2-h peak level significantly higher in patients $<$ 120 kg and $>$ 120 kg ($p = 0.005$), but similar at 4 h AUC for apixaban anti-Xa was significantly lower in patients over 120 kg	Statistically significant reduction in peak levels and overall exposure to apixaban in patients $>$ 120 kg

Abbreviations: AF, atrial fibrillation; AUC, area under the concentration-time curve; BMI, body mass index (kg/m^2); CI, confidence interval; Cmax, maximum plasma concentration; CRNM, clinically relevant non-major bleeding; DVT, deep venous thrombosis; HR, hazard ratio; MI, myocardial infarction; NR, not reported; NS, non-significant; OR, odds ratio; PE, pulmonary embolism; RCT, randomized, controlled trial; SEE, systemic embolic event; TIA, transient ischemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Kushnir et al included 795 patients with AF or VTE and a BMI $\geq 40\ kg/m^2$, and no difference was seen for efficacy or safety when rivaroxaban/apixaban was compared with warfarin.[69] Recently, two large reviews of U.S. health care claims databases were published on morbidly obese patients (BMI $\geq 40\ kg/m^2$) with VTE and AF, respectively.[70,71] The two studies included 2,890 (VTE) and 3,563 (AF) matched pairs on rivaroxaban and warfarin. No differences in clinical efficacy or safety were observed. The warfarin and rivaroxaban-treated patients were matched according to demographics and baseline data, including CHA_2DS_2-VASc score and relevant comorbidities, and this notion may serve to minimize some of the inherent flaws of the retrospective study design. Unfortunately, no detailed information on dosage and renal function were available in these studies.

An additional number of smaller retrospective studies on patients with AF and/or VTE also evaluated the effect of NOAC in patients with BMI $> 40\ kg/m^2$ or body weight > 120 kg and found similar efficacy and safety in comparison with warfarin.[72–74] Other studies found similar efficacy and safety of NOAC in obese patients compared with normal weight patients.[75–77] The majority of patients in the identified retrospective studies were treated with rivaroxaban or apixaban, whereas only four studies included a low proportion (10–30%) of patients on dabigatran, and none of the studies included patients on edoxaban.

Another group of studies mainly evaluated biochemical efficacy and pharmacokinetic properties of NOAC. In general, trough levels of apixaban and rivaroxaban were similar in obese (> 120 kg) and nonobese patients.[76,78,79] On the other hand, Upreti et al and Wasan et al found lower peak levels and over-all drug exposure of apixaban in obese patients.[79,80] However, the observed reductions of apixaban exposure were moderate and unlikely to require dose adjustments. The study by Piran et al included as few as 10 patients on dabigatran,[78] but otherwise, no studies investigating biochemical efficacy were identified for dabigatran or edoxaban.

The interaction between the treatment effect of NOAC and obesity has also been the topic of two previous meta-analyses. Zhou et al evaluated the effect of NOAC in patients with AF and found that these drugs have better efficacy and safety profiles than warfarin in both normal weight and overweight (BMI ≥ 25–$30\ kg/m^2$) patients and are not inferior to warfarin in obese (BMI $\geq 30\ kg/m^2$) patients.[81] Boonyawat et al assessed the effect of body weight on efficacy and safety outcomes in phase III RCTs of NOAC and found no effect of high body weight (> 100 kg).[82] Unfortunately, these meta-analyses did not further stratify obese patients into different BMI classes, and the validity of their conclusions for morbidly obese patients (BMI $\geq 40\ kg/m^2$) remains unclear.

In conclusion, several studies have now evaluated the effect of fixed-dose rivaroxaban and apixaban in obese patients with AF or VTE, including morbidly obese patients (BMI $\geq 40\ kg/m^2$). None of the studies observed reduced clinical efficacy or safety of these drugs in comparison with warfarin or normal weight patients. Hence, no dose adjustment seems to be necessary as a consequence of obesity. We therefore suggest that the current caution on their use in patients weighing > 120 kg or with BMI $\geq 40\ kg/m^2$ should be eased. However, further prospective studies are still warranted. On the other hand, the data on clinical efficacy and safety of dabigatran and edoxaban in obese patients are limited, and these drugs should, therefore, still be avoided.

Fondaparinux Used for Prophylaxis or Treatment

One RCT and one retrospective study evaluated fondaparinux as thromboprophylaxis in bariatric surgery and mixed inpatients, respectively (►**Table 6**).

Steele et al performed an RCT on an increased dose of fondaparinux (5 mg once daily) versus enoxaparin 40 mg twice daily for thromboprophylaxis following bariatric surgery (mean BMI, 45.7 vs. 45.1 kg/m^2).[83] Similar bleeding and VTE rates were observed, but fondaparinux was much more likely to result in the desired prophylactic anti-Xa level than enoxaparin. Martinez et al evaluated the standard prophylactic dose of fondaparinux 2.5 mg once daily for a mixed group of inpatients with a mean BMI of 51.2 kg/m^2.[84] No VTE and only few bleeding episodes were observed. However, 43% of patients had anti-Xa levels below the prophylactic range.

As regards treatment, one post hoc analysis of the Matisse RCTs on fondaparinux for the initial treatment of VTE was identified (►**Table 6**).

In the Matisse trials, fondaparinux was compared with enoxaparin for the initial treatment of VTE until treatment with warfarin was initiated.[85] Four hundred and ninety-six patients > 100 kg received 10 mg once daily and were compared with 3,917 patients ≤ 100 kg receiving the standard dose of 7.5 mg once daily. The treatments were found to be equal as regards VTE recurrence and bleeding in both weight groups.

Based on the limited, but high-quality evidence on fondaparinux, the fixed doses of fondaparinux should probably be increased in patients weighing > 100 kg. Obese patients may potentially benefit from 5 mg once daily for prophylaxis and 10 mg once daily for treatment, but further research is warranted.

Limitations

Several of the included studies primarily evaluated the biochemical efficacy of LMWH, and several precautions should be made in this regard. First, whereas the recommended anti-Xa target ranges for treatment doses are widely accepted in the literature, the corresponding ranges for prophylactic usage are poorly defined.[86] Consequently, the anti-Xa target ranges utilized in the prophylactic studies varied, and the same ranges were generally used for once and twice daily administrations, which appears inappropriate. Second, numerous studies have shown weak relationship between anti-Xa levels and clinical effect or bleeding as critically reviewed by Egan and Ensom. Moreover, the authors found no differences in pharmacokinetics or clinical outcome between obese and nonobese patients and concluded that routine monitoring of anti-Xa in obese patients is not warranted based on the current evidence.[87] Third, the anti-Xa assays varied between the included studies.

Table 6 Studies investigating fondaparinux for thromboprophylaxis or treatment in obese patients

Year, author	Study characteristics Design Patients Follow-up Indication	Treatment Medication, daily dose, duration	Endpoints Clinical efficacy Biochemical efficacy Safety	Results Clinical efficacy Biochemical efficacy Safety	Authors' conclusion
Thromboprophylaxis ($n = 2$)					
Randomized controlled trial					
2015, Steele et al[83]	RCT BMI 35–59 (mean BMI 45.4), $n = 198$ Follow-up: 2 wk Thromboprophylaxis following bariatric surgery	Preoperative enoxaparin (40 mg once daily) + 40 mg twice daily during hospitalization, $n = 98$ vs. postoperative fondaparinux (5 mg once daily) during hospitalization, $n = 100$	Clinical efficacy DVT within 2 wk Biochemical efficacy Anti-Xa (peak, steady state). Range, enoxaparin: 0.2–0.6 - IU/mL. Fondaparinux: 0.39–0.50 - mg/L Safety Death; perioperative bleeding/complications	Clinical efficacy Enoxaparin vs. fondaparinux: DVT: 2.4 vs. 2.2%, $p = 1.00$ Biochemical efficacy Enoxaparin vs. fondaparinux: Within range: 32.4 vs. 74.2%, $p < 0.001$ Safety Enoxaparin vs. fondaparinux: Minor bleeding: 5.1 vs. 3.0% (NS) No major adverse events	Fondaparinux was much more likely to produce prophylactic anti-factor Xa levels than enoxaparin. Both regimens appear to be equally effective at reducing the risk of DVT
Retrospective cohort studies (chart reviews)					
2011, Martinez et al[84]	Retrospective cohort study (chart review) BMI $\geq$ 40 (mean BMI = 51.2), $n = 45$ Follow-up: 30 d Inpatients, any indication	Fondaparinux, 2.5 mg once daily, duration: NS	Clinical efficacy Thrombotic events Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.3–0.5 mg/L Safety Bleeding	Clinical efficacy No thrombotic events Biochemical efficacy Within range: 43% Subtherapeutic: 47% Supratherapeutic: 11% Higher serum creatinine levels were observed in supratherapeutic group ($p = 0.02$). Safety 1 minor bleeding + 1 gastrointestinal bleeding (day 29) (both patients within anti-Xa range)	Anti-Xa levels in morbidly obese patients receiving fondaparinu× 2.5 mg once daily for VTE prophylaxis were within or above the range in 53% of the instances evaluated. Patients with supratherapeutic levels had higher serum creatinine
Treatment ($n = 1$)					
2007, Davidson et al[85]	Post hoc analysis of Matisse trials (RCTs) $>$ 100 kg (mean 110 kg), $n = 496$ $\leq$ 100 kg, $n = 3{,}917$ Follow-up: 90 d VTE	Fondaparinux for $\geq$ 5 d followed by VKA: $>$ 100 kg: 10 mg once daily 50–100 kg: 7.5 mg once daily vs. enoxaparin 1 mg/kg twice daily (DVT) or UFH (PE) for $\geq$ 5 d followed by VKA	Clinical efficacy VTE recurrence Biochemical efficacy NR Safety Major bleeding	Clinical efficacy VTE recurrence: Fondaparinux vs. heparin: $>$ 100 kg: 4.0 vs. 5.7%, $p = 0.41$ $\leq$ 100 kg: 3.9 vs. 4.4%, $p = 0.42$. Safety Major bleeding: Fondaparinux vs. heparins $>$ 100 kg: 0.4 to 0.8%, $p = 0.62$ $\leq$ 100 kg: 1.3% vs. 1.2%, $p = 0.41$	The current recommended doses of fondaparinux and heparins for the initial treatment of VTE appear to provide similar protection against recurrence and major bleeding to one another and to obese and non-obese patients

Abbreviations: BMI, body mass index (kg/m^2); DVT, deep venous thrombosis; NR, not reported; NS, nonsignificant; PE, pulmonary embolism; RCT, randomized, controlled trial; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Although manufacturers ought to calibrate their anti-Xa assays against the World Health Organization standard,[88] different assays have been shown not to result in equivalent anti-Xa levels for the same samples.[89,90] However, anti-Xa levels show great interindividual variation, which result in wide target ranges,[88] and this circumstance may to some degree render poor assay standardization of minor importance. Generally, the topic remains inadequately explored. Therefore, the biochemical evidence should be interpreted with those reservations in mind.

Another limitation relates to variation in the implemented weight or BMI stratifications. Some studies recruited and stratified patients based on certain body weight criteria, whereas other studies utilized BMI and these measures are not directly convertible. Particularly, numerous studies only included a limited number of morbidly obese patients, and this shortcoming impeded subgroup analyses of patients belonging to the highest BMI classes in the affected studies.

Finally, kidney function is an essential parameter, since all of the anticoagulants in question are excreted renally. Yet, not all studies provided data on kidney function and whether patients with renal failure were excluded. Impaired kidney function may cause higher anti-Xa levels and increased risk of bleeding due to accumulation. Any differences in average kidney function between the populations studied may impair the comparability of study outcomes on these measures.

The above-mentioned limitations led to great heterogeneity between studies, and it was, therefore, not possible to conduct a reliable meta-analysis.

Recommendations

Based on the 72 identified studies, the following dosages are recommended:

- LMWH as thromboprophylaxis in bariatric surgery: for patients with BMI < 40 kg/m^2, the recommended fixed dose of enoxaparin 40 mg once daily may be administered. For BMI ≥ 40 kg/m^2, the dose should be increased to 40 mg twice daily. The data on other types of LMWH is limited, but dalteparin 5,000 IU twice daily or tinzaparin 75 IU/kg once daily may be considered in morbidly obese patients. In low-risk patients, LMWH may be administered during hospitalization only, whereas high-risk patients (e.g., previous VTE, strong family history of VTE, and severe thrombophilia) are likely to benefit from an extended treatment of 10 to 15 days after discharge.
- LMWH as thromboprophylaxis in nonbariatric surgery and medical inpatients: the available limited data support the use of enoxaparin 0.5 mg/kg once or twice daily or tinzaparin 75 IU/kg once daily in obese patients.
- LMWH as treatment: for patients with BMI < 40 kg/m^2, the recommended weight-based dose of enoxaparin 1 - mg/kg twice daily may be administered. For BMI ≥ 40 - kg/m^2, the weight-based enoxaparin dose should be reduced to 0.8 mg/kg twice daily. The data on dalteparin and tinzaparin is scarce, but studies indicate that no dose capping should be applied in patients weighing < 140 kg.
- NOAC for thromboprophylaxis following surgery: for patients with BMI < 40 kg/m^2, the limited available evidence supports the use of dabigatran, apixaban, or rivaroxaban in recommended doses. However, no evidence is available for morbidly obese patients, and LMWH should be used instead if BMI exceeds 40 kg/m^2.
- NOAC for VTE or AF: the clinical efficacy and safety of rivaroxaban and apixaban do not seem to be impaired in obese and morbidly obese patients, and therapeutic standard doses of rivaroxaban and apixaban may be administered even to patients with BMI ≥ 40 kg/m^2. The data on dabigatran and edoxaban in obese patients is scarce, and these drugs should still be avoided.
- Fondaparinux: based on the limited evidence available, the fixed doses of fondaparinux should be increased in patients weighing > 100 kg to 10 mg once daily for treatment and 5 mg once daily for prophylaxis, but further research is warranted.

Conflict of Interest
None declared.

References

1 Obesity and overweight (fact sheet). World Health Organization. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed February 23, 2020
2 Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 2008;117(01):93–102
3 Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. Am J Med 2005;118(05):489–495
4 Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. Clin Pharmacokinet 2010; 49(02):71–87
5 Klexane (summary of product characteristics). Available at: https://www.medicines.org.uk. Accessed December 20, 2019
6 Innohep (summary of product characteristics). Available at: https://www.medicines.org.uk. Accessed December 20, 2019
7 Fragmin (summary of product characteristics). Available at: https://www.medicines.org.uk. Accessed December 20, 2019
8 Steib A, Degirmenci SE, Junke E, et al. Once versus twice daily injection of enoxaparin for thromboprophylaxis in bariatric surgery: effects on antifactor Xa activity and procoagulant microparticles. A randomized controlled study. Surg Obes Relat Dis 2016;12(03):613–621
9 Celik F, Huitema AD, Hooijberg JH, van de Laar AW, Brandjes DP, Gerdes VE. Fixed-dose enoxaparin after bariatric surgery: the influence of body weight on peak anti-Xa levels. Obes Surg 2015; 25(04):628–634
10 Gelikas S, Eldar SM, Lahat G. Anti-factor Xa levels in patients undergoing laparoscopic sleeve gastrectomy: 2 different dosing regimens of enoxaparin. Surg Obes Relat Dis 2017;13(10):1753–1759
11 Khoursheed M, Al-Bader I, Al-Asfar F, et al. Therapeutic effect of low-molecular weight heparin and incidence of lower limb deep venous thrombosis and pulmonary embolism after laparoscopic bariatric surgery. Surg Laparosc Endosc Percutan Tech 2013;23 (06):491–493
12 Brunetti L, Wassef A, Sadek R, et al. Anticoagulant activity of enoxaparin and unfractionated heparin for venous thromboembolism prophylaxis in obese patients undergoing sleeve gastrectomy. Surg Obes Relat Dis 2019;15(03):363–373

13 Borkgren-Okonek MJ, Hart RW, Pantano JE, et al. Enoxaparin thromboprophylaxis in gastric bypass patients: extended duration, dose stratification, and antifactor Xa activity. Surg Obes Relat Dis 2008;4(05):625–631
14 Rottenstreich A, Elazary R, Kalish Y. Abdominal thrombotic complications following bariatric surgery. Surg Obes Relat Dis 2017;13(01):78–84
15 Raftopoulos I, Martindale C, Cronin A, Steinberg J. The effect of extended post-discharge chemical thromboprophylaxis on venous thromboembolism rates after bariatric surgery: a prospective comparison trial. Surg Endosc 2008;22(11):2384–2391
16 Escalante-Tattersfield T, Tucker O, Fajnwaks P, Szomstein S, Rosenthal RJ. Incidence of deep vein thrombosis in morbidly obese patients undergoing laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2008;4(02):126–130
17 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(01):19–24
18 Singh K, Podolsky ER, Um S, et al. Evaluating the safety and efficacy of BMI-based preoperative administration of low-molecular-weight heparin in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. Obes Surg 2012;22(01):47–51
19 Rowan BO, Kuhl DA, Lee MD, Tichansky DS, Madan AK. Anti-Xa levels in bariatric surgery patients receiving prophylactic enoxaparin. Obes Surg 2008;18(02):162–166
20 Simone EP, Madan AK, Tichansky DS, Kuhl DA, Lee MD. Comparison of two low-molecular-weight heparin dosing regimens for patients undergoing laparoscopic bariatric surgery. Surg Endosc 2008;22(11):2392–2395
21 Ojo P, Asiyanbola B, Valin E, Reinhold R. Post discharge prophylactic anticoagulation in gastric bypass patient-how safe? Obes Surg 2008;18(07):791–796
22 Paige JT, Gouda BP, Gaitor-Stampley V, et al. No correlation between anti-factor Xa levels, low-molecular-weight heparin, and bleeding after gastric bypass. Surg Obes Relat Dis 2007;3 (04):469–475
23 Leeman M, Biter LU, Apers JA, et al. A single-center comparison of extended and restricted thromboprophylaxis with LMWH after metabolic surgery. Obes Surg 2020;30(02):553–559
24 Magee CJ, Barry J, Javed S, Macadam R, Kerrigan D. Extended thromboprophylaxis reduces incidence of postoperative venous thromboembolism in laparoscopic bariatric surgery. Surg Obes Relat Dis 2010;6(03):322–325
25 Simoneau MD, Vachon A, Picard F. Effect of prophylactic dalteparin on anti-factor Xa levels in morbidly obese patients after bariatric surgery. Obes Surg 2010;20(04):487–491
26 Gaborit B, Moulin PA, Bege T, et al. Lean body weight is the best scale for venous thromboprophylaxis algorithm in severely obese patients undergoing bariatric surgery. Pharmacol Res 2018; 131:211–217
27 Tseng EK, Kolesar E, Handa P, et al. Weight-adjusted tinzaparin for the prevention of venous thromboembolism after bariatric surgery. J Thromb Haemost 2018;16(10):2008–2015
28 Venclauskas L, Maleckas A, Arcelus JIESA VTE Guidelines Task Force. European guidelines on perioperative venous thromboembolism prophylaxis: Surgery in the obese patient. Eur J Anaesthesiol 2018;35(02):147–153
29 Al Otaib N, Bootah Z, Al Ammari MA, et al. Assessment of anti-factor Xa activity of enoxaparin for venous thromboembolism prophylaxis in morbidly obese surgical patients. Ann Thorac Med 2017;12(03):199–203
30 Ludwig KP, Simons HJ, Mone M, Barton RG, Kimball EJ. Implementation of an enoxaparin protocol for venous thromboembolism prophylaxis in obese surgical intensive care unit patients. Ann Pharmacother 2011;45(11):1356–1362
31 Miranda S, Le Cam-Duchez V, Benichou J, et al. Adjusted value of thromboprophylaxis in hospitalized obese patients: A comparative study of two regimens of enoxaparin: The ITOHENOX study. Thromb Res 2017;155:1–5
32 Rostas JW, Brevard SB, Ahmed N, et al. Standard dosing of enoxaparin for venous thromboembolism prophylaxis is not sufficient for most patients within a trauma intensive care unit. Am Surg 2015;81(09):889–892
33 Bickford A, Majercik S, Bledsoe J, et al. Weight-based enoxaparin dosing for venous thromboembolism prophylaxis in the obese trauma patient. Am J Surg 2013;206(06):847–851, discussion 851–852
34 Freeman A, Horner T, Pendleton RC, Rondina MT. Prospective comparison of three enoxaparin dosing regimens to achieve target anti-factor Xa levels in hospitalized, medically ill patients with extreme obesity. Am J Hematol 2012;87(07):740–743
35 Rondina MT, Wheeler M, Rodgers GM, Draper L, Pendleton RC. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-Ill patients. Thromb Res 2010;125(03): 220–223
36 Hainer JW, Barrett JS, Assaid CA, et al. Dosing in heavy-weight/-obese patients with the LMWH, tinzaparin: a pharmacodynamic study. Thromb Haemost 2002;87(05):817–823
37 Kucher N, Leizorovicz A, Vaitkus PT, et al. Efficacy and safety of fixed low-dose dalteparin in preventing venous thromboembolism among obese or elderly hospitalized patients: a subgroup analysis of the PREVENT trial. Arch Intern Med 2005;165(03): 341–345
38 Spinler SA, Inverso SM, Cohen M, Goodman SG, Stringer KA, Antman EMESSENCE and TIMI 11B Investigators. 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(01):33–41
39 Curry MA, LaFollette JA, Alexander BR, Evans KS, Tran RH, Kempton CL. Evaluation of treatment-dose enoxaparin in acutely ill morbidly obese patients at an academic medical center: a randomized clinical trial. Ann Pharmacother 2019;53(06): 567–573
40 Barras MA, Duffull SB, Atherton JJ, Green B. Individualized dosing of enoxaparin for subjects with renal impairment is superior to conventional dosing at achieving therapeutic concentrations. Ther Drug Monit 2010;32(04):482–488
41 Thompson-Moore NR, Wanat MA, Putney DR, Liebl PH, Chandler WL, Muntz JE. Evaluation and pharmacokinetics of treatment dose enoxaparin in hospitalized patients with morbid obesity. Clin Appl Thromb Hemost 2015;21(06):513–520
42 Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. Thromb Res 2005; 116(01):41–50
43 Czupryn MJ, Exline C. Dosing of enoxaparin in morbidly obese patients: a retrospective cohort. Hosp Pharm 2018;53(05): 331–337
44 Spinler SA, Ou FS, Roe MT, et al. Weight-based dosing of enoxaparin in obese patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE initiative. Pharmacotherapy 2009;29(06):631–638
45 Hagopian JC, Riney JN, Hollands JM, Deal EN. Assessment of bleeding events associated with short-duration therapeutic enoxaparin use in the morbidly obese. Ann Pharmacother 2013;47 (12):1641–1648
46 Deal EN, Hollands JM, Riney JN, Skrupky LP, Smith JR, Reichley RM. Evaluation of therapeutic anticoagulation with enoxaparin and associated anti-Xa monitoring in patients with morbid obesity: a case series. J Thromb Thrombolysis 2011;32(02): 188–194
47 Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thromb Thrombolysis 2015;39(04):516–521

48 Lee YR, Palmere PJ, Burton CE, Benavides TM. Stratifying therapeutic enoxaparin dose in morbidly obese patients by BMI class: a retrospective cohort study. Clin Drug Investig 2019;40(01):33–40
49 Lee YR, Vega JA, Duong HN, Ballew A. Monitoring enoxaparin with antifactor Xa levels in obese patients. Pharmacotherapy 2015;35 (11):1007–1015
50 van Oosterom N, Winckel K, Barras M. Evaluation of weight based enoxaparin dosing on anti-Xa concentrations in patients with obesity. J Thromb Thrombolysis 2019;48(03):387–393
51 Maclachlan KH, Stevens HP, Tran HA, Chunilal SD. Weight-based enoxaparin for venous thromboembolism in obesity gives similar anti-Xa levels to patients <100 kg, with no increase in major bleeding. Semin Thromb Hemost 2019;45(01):94–99
52 Sanderink GJ, Le Liboux A, Jariwala N, et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther 2002;72(03):308–318
53 Al-Yaseen E, Wells PS, Anderson J, Martin J, Kovacs MJ. The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients. J Thromb Haemost 2005;3(01):100–102
54 Barrett JS, Gibiansky E, Hull RD, et al. Population pharmacodynamics in patients receiving tinzaparin for the prevention and treatment of deep vein thrombosis. Int J Clin Pharmacol Ther 2001;39(10):431–446
55 McCaughan GJB, Favaloro EJ, Pasalic L, Curnow J. Anticoagulation at the extremes of body weight: choices and dosing. Expert Rev Hematol 2018;11(10):817–828
56 Eriksson BI, Dahl OE, Feuring M, et al. Dabigatran is effective with a favourable safety profile in normal and overweight patients undergoing major orthopaedic surgery: a pooled analysis. Thromb Res 2012;130(05):818–820
57 Pineo GF, Gallus AS, Raskob GE, et al. Apixaban after hip or knee arthroplasty versus enoxaparin: efficacy and safety in key clinical subgroups. J Thromb Haemost 2013;11(03):444–451
58 Krauss ES, Cronin M, Dengler N, et al. The effect of BMI and gender on bleeding events when rivaroxaban is administered for thromboprophylaxis following total hip and total knee arthroplasty. Semin Thromb Hemost 2019;45(02):180–186
59 Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol 2007;47(02):218–226
60 Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14 (06):1308–1313
61 Balla SR, Cyr DD, Lokhnygina Y, et al. Relation of risk of stroke in patients with atrial fibrillation to body mass index (from patients treated with rivaroxaban and warfarin in the rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation trial). Am J Cardiol 2017;119(12):1989–1996
62 Di Nisio M, Vedovati MC, Riera-Mestre A, et al. Treatment of venous thromboembolism with rivaroxaban in relation to body weight. A sub-analysis of the EINSTEIN DVT/PE studies. Thromb Haemost 2016;116(04):739–746
63 Boriani G, Ruff CT, Kuder JF, et al. Relationship between body mass index and outcomes in patients with atrial fibrillation treated with edoxaban or warfarin in the ENGAGE AF-TIMI 48 trial. Eur Heart J 2019;40(19):1541–1550
64 Lip GYH, Merino JL, Banach M, et al. Impact of body mass index on outcomes in the edoxaban versus warfarin therapy groups in patients underwent cardioversion of atrial fibrillation (from ENSURE-AF). Am J Cardiol 2019;123(04):592–597
65 Sandhu RK, Ezekowitz J, Andersson U, et al. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) trial. Eur Heart J 2016;37(38):2869–2878
66 Hohnloser SH, Fudim M, Alexander JH, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and extremes in body weight. Circulation 2019;139(20): 2292–2300
67 Reilly PA, Lehr T, Haertter S, et al; RE-LY Investigators. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 2014;63 (04):321–328
68 Tittl L, Endig S, Marten S, Reitter A, Beyer-Westendorf I, Beyer-Westendorf J. Impact of BMI on clinical outcomes of NOAC therapy in daily care - results of the prospective Dresden NOAC Registry (NCT01588119). Int J Cardiol 2018;262:85–91
69 Kushnir M, Choi Y, Eisenberg R, et al. Efficacy and safety of direct oral factor Xa inhibitors compared with warfarin in patients with morbid obesity: a single-centre, retrospective analysis of chart data. Lancet Haematol 2019;6(07):e359–e365
70 Peterson ED, Ashton V, Chen YW, Wu B, Spyropoulos AC. Comparative effectiveness, safety, and costs of rivaroxaban and warfarin among morbidly obese patients with atrial fibrillation. Am Heart J 2019;212:113–119
71 Spyropoulos AC, Ashton V, Chen YW, Wu B, Peterson ED. Rivaroxaban versus warfarin treatment among morbidly obese patients with venous thromboembolism: Comparative effectiveness, safety, and costs. Thromb Res 2019;182:159–166
72 Kalani C, Awudi E, Alexander T, Udeani G, Surani S. Evaluation of the efficacy of direct oral anticoagulants (DOACs) in comparison to warfarin in morbidly obese patients. Hosp Pract 1995; 2019:1–5
73 Kido K, Ngorsuraches S. Comparing the efficacy and safety of direct oral anticoagulants with warfarin in the morbidly obese population with atrial fibrillation. Ann Pharmacother 2019;53 (02):165–170
74 Perales IJ, San Agustin K, DeAngelo J, Campbell AM. Rivaroxaban versus warfarin for stroke prevention and venous thromboembolism treatment in extreme obesity and high body weight. Ann Pharmacother 2019 (e-pub ahead of print) . Doi: 10.1177/1060028019886092
75 Aloi KG, Fierro JJ, Stein BJ, Lynch SM, Shapiro RJ. Investigation of direct-acting oral anticoagulants and the incidence of venous thromboembolism in patients weighing ≥120 kg compared to patients weighing <120 kg. J Pharm Pract 2019 (e-pub ahead of print) . Doi: 10.1177/897190019854578
76 Arachchillage D, Reynolds R, Devey T, Maclean R, Kitchen S, van Veen JJ. Effect of extremes of body weight on drug level in patient treated with standard dose of rivaroxaban for venous thromboembolism; real life experience. Thromb Res 2016; 147:32–35
77 Netley J, Howard K, Wilson W. Effects of body mass index on the safety and effectiveness of direct oral anticoagulants: a retrospective review. J Thromb Thrombolysis 2019;48(03): 359–365
78 Piran S, Traquair H, Chan N, Bhagirath V, Schulman S. Peak plasma concentration of direct oral anticoagulants in obese patients weighing over 120 kilograms: A retrospective study. Res Pract Thromb Haemost 2018;2(04):684–688
79 Wasan SM, Feland N, Grant R, Aston CE. Validation of apixaban anti-factor Xa assay and impact of body weight. Thromb Res 2019; 182:51–55
80 Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol 2013;76(06):908–916
81 Zhou Y, Ma J, Zhu W. Efficacy and safety of direct oral anticoagulants versus warfarin in patients with atrial fibrillation across BMI categories: a systematic review and meta-analysis. Am J Cardiovasc Drugs 2020;20(01):51–60

82 Boonyawat K, Caron F, Li A, et al. Association of body weight with efficacy and safety outcomes in phase III randomized controlled trials of direct oral anticoagulants: a systematic review and meta-analysis. J Thromb Haemost 2017;15(07):1322–1333
83 Steele KE, Canner J, Prokopowicz G, et al. The EFFORT trial: Preoperative enoxaparin versus postoperative fondaparinux for thromboprophylaxis in bariatric surgical patients: a randomized double-blind pilot trial. Surg Obes Relat Dis 2015;11(03):672–683
84 Martinez L, Burnett A, Borrego M, Streeter JC, Townsend K, Garcia D. Effect of fondaparinux prophylaxis on anti-factor Xa concentrations in patients with morbid obesity. Am J Health Syst Pharm 2011;68(18):1716–1722
85 Davidson BL, Büller HR, Decousus H, et al; Matisse Investigators. Effect of obesity on outcomes after fondaparinux, enoxaparin, or heparin treatment for acute venous thromboembolism in the Matisse trials. J Thromb Haemost 2007;5(06):1191–1194
86 Wei MY, Ward SM. The anti-factor Xa range for low molecular weight heparin thromboprophylaxis. Hematol Rep 2015;7(04):5844
87 Egan G, Ensom MH. Measuring anti-factor xa activity to monitor low-molecular-weight heparin in obesity: a critical review. Can J Hosp Pharm 2015;68(01):33–47
88 Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: the clinical use and laboratory monitoring of low-molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. Arch Pathol Lab Med 1998;122(09):799–807
89 Kovacs MJ, Keeney M, MacKinnon K, Boyle E. Three different chromogenic methods do not give equivalent anti-Xa levels for patients on therapeutic low molecular weight heparin (dalteparin) or unfractionated heparin. Clin Lab Haematol 1999;21(01):55–60
90 Kitchen S, Iampietro R, Woolley AM, Preston FE. Anti Xa monitoring during treatment with low molecular weight heparin or danaparoid: inter-assay variability. Thromb Haemost 1999;82(04):1289–1293