

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

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Semin Thromb Hemost 2020;46:932–969.

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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] ≥ 30 kg/m² or body weight ≥ 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 ≥ 40 kg/m². 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 ≥ 40 kg/m², 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/m² ($n = 4$ studies), whereas rivaroxaban and apixaban may be administered to obese patients with VTE or AF, including BMI > 40 kg/m², 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) ≥ 30 kg/m² is typically considered obese, whereas morbid obesity is defined as BMI ≥ 40 kg/m².¹ 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).

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 ≥ 100 kg or with BMI ≥ 30 kg/m²; (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 ≤ 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 "rivaroxaban"/exp OR "rivaroxaban" OR "apixaban"/exp OR apixaban OR "edoxaban"/exp OR edoxaban OR "dabigatran etexilate"/exp OR "dabigatran etexilate" OR "dabigatran"/exp OR "dabigatran" OR "fondaparinux")	

Abbreviations: LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist oral anticoagulants.

^aFilters applied in Embase: "human"/de AND ("article"/it OR "article in press"/it OR "letter"/it).

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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

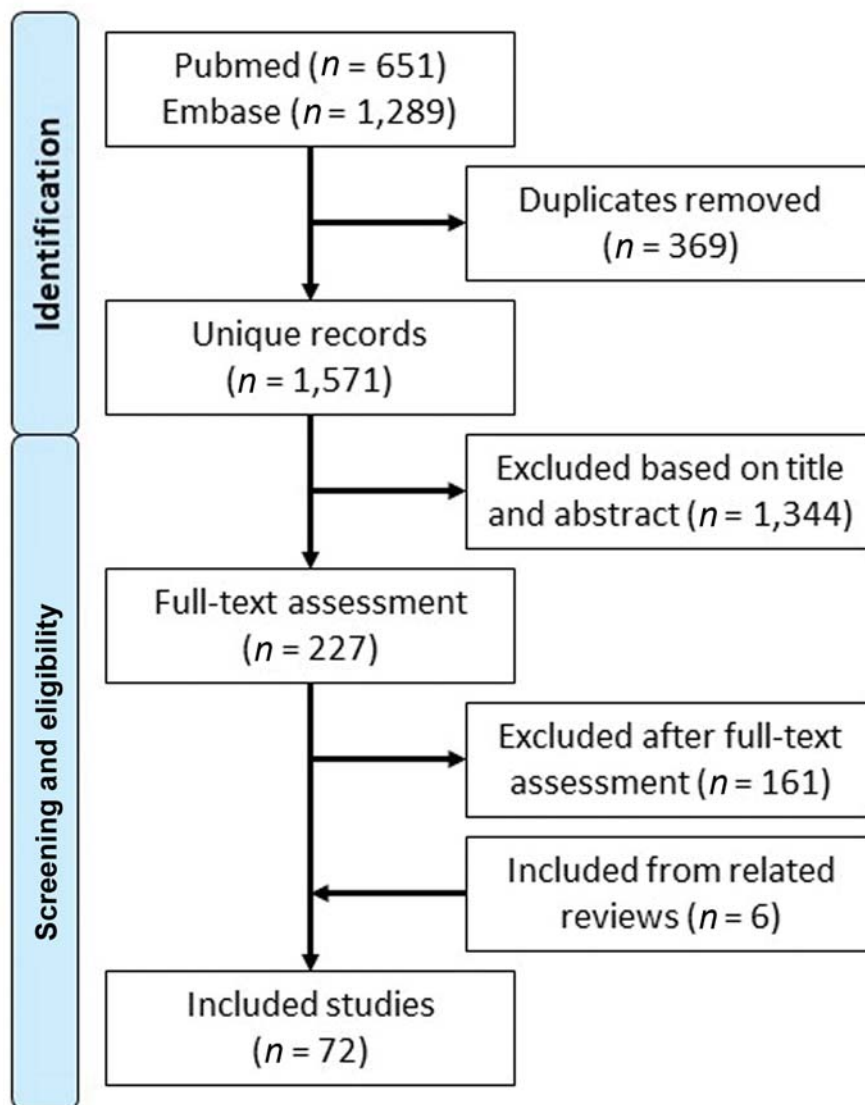


Fig. 1 Flowchart describing the selection process of articles.

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)					
<i>Randomized controlled trials</i>					
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	<u>Clinical efficacy</u> DVT Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.3–0.5 IU/mL <u>Safety</u> Perioperative bleeding	<u>Clinical efficacy</u> 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) <u>Safety</u> 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
<i>Prospective cohort studies</i>					
2008, Borkgren-Olkonet 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	<u>Clinical efficacy</u> VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.2–0.4 IU/mL <u>Safety</u> Bleeding	<u>Clinical efficacy</u> 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% <u>Safety</u> 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 units 120	<u>Clinical efficacy</u> VTE Biochemical efficacy Anti-Xa (peak, steady state). Range: 0.1–0.5 IU/mL.	<u>Clinical efficacy</u> 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

(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
		(kg) × 3 daily, n = 44, initiated 2–3 h preoperatively, duration NR	<u>Safety</u> Bleeding	<u>Safety</u> 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	<u>Clinical efficacy</u> Thrombotic events <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL <u>Safety</u> Bleeding	<u>Clinical efficacy</u> No events <u>Biochemical efficacy</u> < 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 <u>Safety</u> 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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL <u>Safety</u> Bleeding	<u>Clinical efficacy</u> No events <u>Biochemical efficacy</u> 40-mg vs. 60-mg; Mean anti-Xa: 0.247 IU/mL vs. 0.346 IU/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
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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.2–0.6 U/mL <u>Safety</u> Bleeding	C^2 test: $p = 0.016$ <u>Safety</u> 60 mg: 1 excessive bleeding during surgery <u>Clinical efficacy</u> No events in study population. 1 fatal PE in all dept.'s bariatric patients (0.09%) <u>Biochemical efficacy</u> 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% <u>Safety</u> No bleeding	Enoxaparin 40 mg once daily may be insufficient in obese bariatric patients with less than 50% reaching anti-Xa range
<i>Retrospective cohort studies (chart reviews)</i>					
2008, Escalante-Tattersfield et al ¹⁶	Retrospective cohort study (chart review) BMI $\geq 35 + \geq 2$ comorbid conditions, or BMI ≥ 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)	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> NR <u>Safety</u> Bleeding episodes, HIT	<u>Clinical efficacy</u> DVT: 0.16% (1 event) <u>Safety</u> 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 ≥ 50 and comorbidity, n = 84 BMI ≥ 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	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> NR <u>Safety</u> Bleeding or decrease in hematocrit	<u>Safety</u> No major bleedings. No decrease in hematocrit to critical levels	Both enoxaparin regimens were safe in obese with BMI ≥ 50
2007, Paige et al ²²	Retrospective cohort study (chart review) BMI ≥ 35 and	Enoxaparin 1 mg/BMI-unit twice daily initiated	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u>	<u>Biochemical efficacy</u> Transfused (data from 58%) vs. not-transfused	Transfusions rate in obese did not vary

(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
	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 <u>Safety</u> Blood transfusions (packed red blood cells, PRBCs)	(data from 82%); Mean anti-Xa: 0.13 IU/mL vs. 0.16 IU/mL, $p = 0.7$ <u>Safety</u> Transfusion rate: 11.7% (transfused, $n = 12$; not 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, $n = 176$	<u>Clinical efficacy</u> VTE within 30 d 30-d morbidity (death, anastomotic leak, hemorrhage, VTE, small bowel obstruction, cardiac/renal/pulmonary complication) <u>Biochemical efficacy</u> NR <u>Safety</u> Bleeding episodes within 30 d	<u>Clinical efficacy</u> 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%, $p = NS$ <u>Safety</u> 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, $n = 543$	<u>Clinical efficacy</u> Thrombotic events (PSMVT, DVT, PE) <u>Biochemical efficacy</u> NR <u>Safety</u> NR	<u>Clinical efficacy</u> 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	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.18–0.44 U/mL	<u>Biochemical efficacy</u> 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
2002, Scholten et al ¹⁷	Retrospective cohort study (chart review) Mean BMI 50.6, n = 481 Follow-up: at least 6 mo	twice daily n = 33, mean BMI = 48.4 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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> NR Safety Bleeding	<u>Clinical efficacy</u> 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	levels. No levels were supratherapeutic 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	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.18–0.44 U/ml <u>Safety</u> Bleeding episodes	<u>Biochemical efficacy</u> 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 <u>Safety</u> 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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> NR <u>Safety</u> Bleeding	<u>Clinical efficacy</u> No VTE <u>Safety</u> 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

(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
Bariatric surgery, dalteparin (n = 4)					
<i>Prospective cohort studies</i>					
2018, Gaborit et al ²⁶	Prospective cohort study BMI ≥ 35 + ≥ 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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL. <u>Safety</u> <u>Bleeding</u>	<u>Clinical efficacy</u> No events <u>Biochemical efficacy</u> Median peak level 0.19 IU/mL (0.13–0.26 IU/mL) Within range: 48% <u>Supratherapeutic</u> : 0.08% <u>Subtherapeutic</u> : 51.92% <u>Safety</u> 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
<i>Retrospective cohort studies (chart reviews)</i>					
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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> NR <u>Safety</u> Postoperative hemorrhage within 1 mo	<u>Clinical efficacy</u> VTE events: 0.07% (extended treatment group) <u>Safety</u> 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)	<u>Clinical efficacy</u> <u>Symptomatic VTE</u> and 30- and 90-d mortality rate <u>Biochemical efficacy</u> NR <u>Safety</u> Bleeding, HIT	<u>Clinical efficacy</u> VTE events: 0 Mortality rate: 0% <u>Safety</u> 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 ≥ 35 with comorbidity or BMI ≥ 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 ≥ 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
<i>Retrospective cohort studies (chart reviews)</i>					
2011, Ludwig et al ³⁰	Retrospective cohort study (chart review) BMI ≥ 35 or ≥ 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)	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.2–0.5 IU/mL <u>Safety</u> Bleeding; HIT	<u>Clinical efficacy</u> VTE: 1 DVT, maybe pre-existing (anti-Xa-level: 0.38 IU/mL on 70 mg enoxaparin) <u>Biochemical efficacy</u> Mean anti-Xa: 0.34 IU/mL Within range: 91% ($n = 21$) Supratherapeutic: $n = 2$ Subtherapeutic: $n = 0$ <u>Safety</u> Minor bleeding: 1 event No major bleeding or HIT	Weight-based dosing with enoxaparin in morbidly obese patients 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 ($n = 5$)					
<i>Randomized controlled trials</i>					
2017, Miranda et al ³¹	RCT Medical inpatients, BMI ≥ 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, $n = 46$	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.32–0.54 IU/mL <u>Safety</u> Major/minor bleeding	<u>Clinical efficacy</u> No events <u>Biochemical efficacy</u> 40 vs. 60 mg: Within range: 31 vs. 69%, $p = 0.007$. Supratherapeutic: NR Subtherapeutic: 64 vs. 36%, $p = 0.001$. <u>Safety</u> 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
<i>Prospective cohort studies</i>					
2013, Bickford et al ³³	Prospective cohort study Trauma patients, BMI ≥ 30 (median BMI = 35.3), $n = 86$ Follow-up, mean: 9.5 d	Enoxaparin, 0.5 mg/kg twice daily, duration: NR	<u>Clinical efficacy</u> VTE (ultrasound screening of all patients) <u>Biochemical efficacy</u> Anti-Xa (peak, steady	<u>Clinical efficacy</u> PE: 0 (0%) DVT: 18 (21%), 16 found before start of enoxaparin. <u>Biochemical efficacy</u>	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
2012, Freeman et al ³⁴	Prospective cohort study Medical inpatients, BMI ≥ 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	<u>Clinical efficacy</u> Symptomatic DVT or PE <u>Biochemical efficacy</u> Anti-Xa (peak, steady-state). Range: 0.2–0.5 IU/mL <u>Safety</u> Bleeding and HIT	Within range: n = 74 (86%) Supratherapeutic: n = 8 Subtherapeutic: n = 4 <u>Safety</u> No bleeding events <u>Clinical efficacy</u> No events <u>Biochemical efficacy</u> Subtherapeutic levels, fixed vs. low-dose vs. high dose: 82 vs. 36 vs. 13%, p < 0.001 One case supratherapeutic (low dose). <u>Safety</u> No events	measured by anti-Xa levels, and appears to be safe without bleeding complications 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 ≥ 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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.2–0.6 IU/mL <u>Safety</u> Bleeding episodes; HIT	<u>Clinical efficacy</u> No events <u>Biochemical efficacy</u> Average peak anti-Xa: 0.25 U/mL, range 0.08–0.59 U/mL <u>Safety</u> 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 ≥ 30, n = 14 BMI < 30, n = 14 Mean BMI 32.3. Follow-up: NR	Enoxaparin, 30 mg twice daily, duration: NR	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Anti-Xa (trough level before 4th dose); subtherapeutic level defined as < 0.1 IU/mL <u>Safety</u> NR	<u>Biochemical efficacy</u> 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;	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Anti-Xa (peak, steady state): Amax, AUC Anti-Ila activity	<u>Biochemical efficacy</u> 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	<u>Safety</u> 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) <u>Safety</u> 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/m²); 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/m² (mean BMI, 48 kg/m²) 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/m² and 60 mg once daily for patients with BMI > 50 kg/m².¹³

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/m².¹⁴ 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/m² without increased risk of bleeding¹⁷; 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/m².^{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/m².²¹ 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/m².²³ 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/m²) 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/m².²⁷ 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/m². 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/m².²⁹ 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/m², 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/m².³² 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/m².^{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 ≥ 28.6 kg/m² for women and ≥ 30 kg/m² for men). The study included 1,118 obese patients (median BMI, 32.9 kg/m²), 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/m². Importantly, the 3.3% of obese patients with BMI ≥ 40 kg/m² 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 ≥ 30 kg/m² (mean BMI, 33.9 kg/m²). Unfortunately, the proportion of morbidly obese patients (BMI ≥ 40 kg/m²) 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/m²).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/m², $n = 41$) 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 ≥ 30 kg/m².⁴² The majority of patients in the latter study had a BMI < 40 kg/m², 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/m²) 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/m² 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 ≥ 40 kg/m² with a low incidence of bleedings and thromboembolic events.^{46,47} Moreover, Lee et al conducted two studies in morbidly obese patients (BMI ≥ 40 kg/m²) 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/m².

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/m².^{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)					
<i>Randomized controlled trials</i>					
2010, Barras et al ⁴⁰	RCT ≥ 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)	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL <u>Safety</u> NR	<u>Biochemical efficacy</u> 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 ≥ 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	<u>Clinical efficacy</u> Recurrent VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.5–1.1 IU/mL) and time to reach target. <u>Safety</u> Major and minor bleeding	<u>Clinical efficacy</u> No thrombotic events <u>Biochemical efficacy</u> 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 <u>Safety</u> 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 ≥ 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	<u>Clinical efficacy</u> Death, myocardial infarction (MI), urgent revascularization (UR) <u>Biochemical efficacy</u> NR <u>Safety</u> Major bleeding and hemorrhage	<u>Clinical efficacy</u> 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 <u>Safety</u> 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)

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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>$p = 0.08$ 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%, $p = 0.004$</p>	
<i>Prospective cohort studies</i>					
2005, Bazinet et al ⁴²	Prospective cohort study BMI ≥ 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, $n = 69$)	<u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 1.0–2.0 IU/mL (once daily) or 0.5–1.1 IU/mL (twice daily) <u>Safety</u> NR	<u>Biochemical efficacy</u> 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 ≥ 40 or ≥ 140 kg (median BMI = 45.6), $n = 41$ Follow-up, median: 5 d Any indication	Recommended, enoxaparin 1 mg/kg (≥ 0.95 mg/kg), $n = 18$ or reduced, enoxaparin 0.95 mg/kg, $n = 23$	<u>Clinical efficacy</u> Thrombotic events <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.6–1.0 IU/mL <u>Safety</u> Bleeding	<u>Clinical efficacy</u> No events <u>Biochemical efficacy</u> 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%, $p = 0.35$ <u>Safety</u> 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
<i>Retrospective cohort studies (chart reviews)</i>					
2018, Czupryn and Exline ⁴³	Retrospective cohort study (chart review) 120 kg (median	Enoxaparin (< 90% of FDA-approved dose), $n = 56$ or enoxaparin (\geq	<u>Clinical efficacy</u> Ischemic stroke, VTE and death <u>Biochemical</u>	<u>Clinical efficacy</u> < 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. ≥ 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, ≥ 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. normal-weight, 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)

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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	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.5–1.1 IU/mL <u>Safety</u> Bleeding	<u>Biochemical efficacy</u> Within range: 50.5% Supratherapeutic: 35.4% Subtherapeutic: 14.1% <u>Safety</u> 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)	<u>Clinical efficacy</u> Thromboembolic events <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL <u>Safety</u> Bleeding	<u>Clinical efficacy</u> 1 thromboembolic event caused by HIT. <u>Biochemical efficacy</u> 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% <u>Safety</u> 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	<u>Clinical efficacy</u> Recurrent VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL. <u>Safety</u> Major and CRNM within 30 d	<u>Clinical efficacy</u> Obese vs. normal weight: 0 vs. 4%, $p = 0.13$ <u>Biochemical efficacy</u> Obese vs. normal weight; Within range: 56 vs. 44%, $p = 0.15$. Supratherapeutic: 40 vs. 45%, $p = 0.99$. Subtherapeutic: 4 vs. 11%, $p = 0.11$ <u>Safety</u> 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 review)	Enoxaparin, recommended dose:	<u>Clinical efficacy</u> NR	<u>Safety</u> 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	<u>Biochemical efficacy</u> NR <u>Safety</u> 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	<u>Clinical efficacy</u> Recurrent VTE <u>Biochemical efficacy</u> Anti-Xa (peak, steady state). Range: 0.5–1.0 IU/mL. <u>Safety</u> Bleeding	<u>Clinical efficacy</u> 2 recurrent VTEs (PE); both with 1 mg/kg twice daily. <u>Biochemical efficacy</u> < 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% <u>Safety</u> 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
<i>Pharmacodynamic studies</i>					
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	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Anti-Xa: Amax and AUC Anti-IIa: AUC <u>Safety</u> Death, major bleeding	<u>Biochemical efficacy</u> 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 <u>Safety</u> 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	<u>Clinical efficacy</u> Recurrent VTE	<u>Clinical efficacy</u> Recurrent VTE: 3	It is safe to administer

(Continued)

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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 effi- cacy 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 thromboembo- lism without an increased risk of major hemorrhage
Tinzaparin ($n = 2$)					
2001, Barrett et al ⁵⁴	Pharmacodynam- ic study BMI < 30, $n = 157$ BMI ≥ 30 , $n = 30$ Follow-up: NR Proximal DVT	Tinzaparin 175 IU/kg once daily	Clinical efficacy NR Biochemical effi- cacy Plasma anti-Xa (pharmacodynam- ic model). Safety NR	Biochemical effi- cacy Body weight was not a significant covariate in the model. Clearance in obese patients de- creased by 22%	The effect of obe- sity is probably not clinically sig- nificant, and no dose capping should be applied
2002, Hainer et al ³⁶	Pharmacodynam- ic 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 tinza- parin 175 IU/kg (prophylactic dose, see ► Table 2)	Clinical efficacy NR Biochemical effi- cacy Anti-Xa: Amax (- IU/mL), AUC (IU* h/mL) Anti-IIa: Amax(- IU/mL), AUC (IU* h/mL) Safety Bleeding events	Biochemical effi- cacy 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 dos- ing in heavy or obese patients is appropriate based on body weight alone; the dose need not be capped at a maxi- mal 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 $\geq 40 \text{ kg}/\text{m}^2$. 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 $\geq 40 \text{ kg}/\text{m}^2$ 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 <u>Biochemical efficacy</u> NR <u>Safety</u> 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. <u>Safety</u> 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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> NR <u>Safety</u> Major bleeding, CRNM bleeding	<u>Clinical efficacy</u> Total events: 74 Apixaban vs. enoxaparin BMI-effect, interaction p = 0.2273 <u>Safety</u> 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
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	<u>Clinical efficacy</u> VTE <u>Biochemical efficacy</u> NR Safety Bleeding	<u>Clinical efficacy</u> Similar number of VTE events in normal weight and obese patients (0.4%). <u>Safety</u> 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, Kubitz 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	<u>Clinical efficacy</u> Not reported <u>Biochemical efficacy</u> Pharmacodynamics and pharmacokinetics <u>Safety</u> Adverse events	<u>Biochemical efficacy</u> No difference in AUC plasma concentration, C _{max} or half-life. <u>Safety</u> 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/m²); CI, confidence interval; C_{max}, 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 ≥ 30 kg/m²) 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 ≥ 40 kg/m². 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 ≥ 30 kg/m²), but no data on the subgroup of patients with BMI ≥ 40 kg/m² was available.⁵⁸ Finally, the pharmacokinetic study by Kubitz 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 ≥ 40 kg/m²).

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 ≥ 40 kg/m²) 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/m².⁶⁰

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 ≥ 35 kg/m², and rivaroxaban was even found superior to warfarin in AF patients with BMI ≥ 35 kg/m² for stroke prevention. Still, no separate analysis on patients with BMI ≥ 40 kg/m² was performed. The ENGAGE AF-TIMI trial on edoxaban for AF included 1,149 patients with a BMI ≥ 40 kg/m².⁶³ 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 ≥ 40 kg/m² (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 ≥ 30 kg/m².⁶⁴ 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 ≥ 40 kg/m².⁶⁵ 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/m²). 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 Tittel 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 ≥ 35 kg/m² and 98 BMI ≥ 40 kg/m². 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 ≥ 30, n = 5,206 (including BMI 35–40, n = 1,278 and BMI ≥ 40, n = 620) Follow-up, median: 2 y AF	Rivaroxaban, 15–20 mg once daily vs. warfarin	<u>Clinical efficacy</u> Stroke or systemic embolism <u>Biochemical efficacy</u> NR <u>Safety</u> Major and CRNM events	<u>Clinical efficacy</u> Rivaroxaban vs. warfarin: BMI effect normal weight vs. overweight vs. obese, interaction: p = 0.40 BMI ≥ 35 vs. normal weight on rivaroxaban: HR = 0.62 (95% CI: 0.40–0.96, p = 0.033) <u>Safety</u> 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 ≥ 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 ≥ 40, n = 1,149	Edoxaban high dose, 60 mg once daily vs. Edoxaban low dose, 30 mg once daily vs. warfarin	<u>Clinical efficacy</u> Stroke or SFE <u>Biochemical efficacy</u> Anti-Xa and plasma edoxaban levels (trough, steady state). <u>Safety</u> Events of major bleeding and major and CRNM	<u>Clinical efficacy</u> 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/SFE, 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			<u>Biochemical efficacy</u> No association between BMI and plasma edoxaban/anti-Xa levels. <u>Safety</u> 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	<u>Clinical efficacy</u> Recurrent VTE <u>Biochemical efficacy</u> NR <u>Safety</u> Major bleeding and clinically relevant bleeding	<u>Clinical efficacy</u> 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. <u>Safety</u> No association between major or clinically relevant bleedings and bodyweight (p = 0.87) or BMI (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	<u>Clinical efficacy</u> Stroke/SEE; death; stroke/SEE/MI/Death <u>Biochemical efficacy</u> NR <u>Safety</u> Major bleeding	<u>Clinical efficacy</u> 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. <u>Safety</u> 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
2019, Lip et al ⁶⁴	Post hoc analysis of EN-SURE-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)	<u>Clinical efficacy</u> Stroke, SEE, MI, and cardiovascular death <u>Biochemical efficacy</u> NR <u>Safety</u> Major and CRNM bleeding	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) <u>Clinical efficacy</u> 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) <u>Safety</u> 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-ILY 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	<u>Clinical efficacy</u> NR <u>Biochemical efficacy</u> Plasma dabigatran concentration <u>Safety</u> NR	<u>Biochemical efficacy</u> 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	<u>Clinical efficacy</u> Stroke/SEE; death; stroke/SEE/MI/Death <u>Biochemical efficacy</u> NR <u>Safety</u> Major bleeding	<u>Clinical efficacy</u> 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
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, 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 efficacy Recurrent 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 Ngorurachues 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
2019, Kushnir et al ⁶⁹	Retrospective cohort study (chart review) BMI ≥ 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	Major bleeding: DOAC vs. warfarin: RR 0.44 (95% CI: 0.15–1.25), p = 0.11 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
2019, Wasan et al ⁷⁹	65–85 kg, n = 18 Follow-up: 72 h Healthy volunteers Pharmacodynamic study ≤ 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	h) Safety Adverse effects <u>Clinical efficacy</u> NR Biochemical efficacy Anti-Xa (trough + peak (2 + 4 h) <u>Safety</u> NR	<u>Safety</u> Adverse effects: 12 (all mild or moderate, no bleeding) Biochemical efficacy Similar trough anti-Xa levels in patients ≤ 120 kg and > 120 kg (p = 0.4). 2-h peak level signifi- cantly 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/m²); 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 ≥ 40 kg/m², 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 ≥ 40 kg/m²) 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 CHA₂DS₂-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/m² 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/m²) patients and are not inferior to warfarin in obese (BMI ≥ 30 kg/m²) 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 ≥ 40 kg/m²) 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 ≥ 40 kg/m²). 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 ≥ 40 kg/m² 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/m²).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/m².⁸⁴ 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)					
<i>Randomized controlled trial</i>					
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
<i>Retrospective cohort studies (chart reviews)</i>					
2011, Martinez et al ⁸⁴	Retrospective cohort study (chart review) BMI ≥ 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 fondaparinux 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
<i>Treatment (n = 1)</i>					
2007, Davidson et al ⁸⁵	Post hoc analysis of Matisse trials (RCTs) > 100 kg (mean 110 kg), n = 496 ≤ 100 kg, n = 3,917 Follow-up: 90 d VTE	Fondaparinux for ≥ 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 ≥ 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 ≤ 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 ≤ 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/m²); 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/m², the recommended fixed dose of enoxaparin 40 mg once daily may be administered. For BMI ≥ 40 kg/m², 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/m², the recommended weight-based dose of enoxaparin 1-mg/kg twice daily may be administered. For BMI ≥ 40 kg/m², 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/m², 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/m².
- 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/m². 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.

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