**What factors should be considered when using low molecular weight heparin (LMWH) to treat venous thromboembolism in patients with high body weight?**

Prepared by UK Medicines Information ([UKMi](http://www.ukmi.nhs.uk/ukmi/about/default.asp?pageRef=1)) pharmacists for NHS healthcare professionals

Before using this Q&A, read the disclaimer at [*https://www.sps.nhs.uk/articles/about-ukmi-medicines-qas/*](https://www.sps.nhs.uk/articles/about-ukmi-medicines-qas/)

Date prepared: June 2020

## Background

It is important to ensure that the correct dose of a low molecular weight heparin (LMWH) is used for the treatment of venous thromboembolism (VTE); both under and overdosing can be associated with serious adverse outcomes. Patients of high body weight have been hugely under-represented in clinical trials and, therefore, the optimal dosing of a LMWH with respect to both safety and efficacy in this subgroup remains unknown.

The Summary of Product Characteristics (SPC) for the LMWHs enoxaparin, dalteparin and tinzaparin state that the treatment dose for VTE should be based on the patient’s weight. The SPCs for enoxaparin and tinzaparin do not make a recommendation on dose capping (1,2) however the SPC for dalteparin states that the daily dose should be no higher than 18000 units regardless of body weight (3). Enoxaparin can be given at a dose of 1.5 mg/kg once daily or 1 mg/kg twice daily and the regimen selected should be based on an individual assessment including evaluation of the thromboembolic risk and of the risk of bleeding. For patients with obesity the 1 mg/kg twice daily dosing strategy is recommended (1). Dalteparin and tinzaparin are administered once daily although the manufacturer of dalteparin recommends that, for patients with an increased risk of bleeding, a dose of 100 IU/kg twice daily should be used (3).

This Q&A offers guidance on what factors should be considered when calculating a LMWH treatment dose following a VTE in non-pregnant adult patients with a high body weight, defined as more than 120 kg. It focuses on enoxaparin, dalteparin and tinzaparin.

## Answer

The factors that should be considered when using a LMWH to treat VTE in high body weight patients include:

1. What weight measure to use when calculating the dose and whether the dose should be capped
2. The frequency of LMWH dosing
3. Monitoring requirements
4. Alternative dosing strategies
5. Practical issues around prescribing and administration

**1. Total body weight or lean body weight**

It is generally accepted that body composition has an impact on how individuals handle drugs (4).

In general terms, total body weight (TBW) has been proposed as the best single descriptor for estimating volume of distribution (Vd) and lean body weight (LBW) as a better predictor of drug clearance (5). No single body size descriptor has been universally accepted for dose adjustment in patients with high body weight and there is conflicting opinion on which descriptor is the most appropriate for dose calculation of LMWHs (5).

LMWHs are hydrophilic compounds (6,7). Their distribution tends to be confined to the intravascular space which is similar to plasma volume (8-10). Patients with high body weight normally have a higher plasma volume than the general population, so it is reasonable to accept that the Vd of LMWHs is increased in this patient population (11). However, this increase is not directly proportional to the TBW (11).

Although no robust data exist, most available evidence suggests that it is safe to use TBW when calculating treatment doses of LMWHs for high body weight patients, and that dose capping should not be used due to the potential underdosing of very large patients and the potentially serious consequences of therapeutic failure (10, 12-14). This approach is off-label for dalteparin as the manufacturer recommends the use of daily doses no higher than 18000 units (3). Available evidence is limited to patients weighing up to 144 kg for enoxaparin, 190 kg for dalteparin and 165 kg for tinzaparin (12,13). A large proportion of the evidence comes from pharmacodynamic studies (15-19). The main limitations of current evidence are the small sample sizes and the use of anti-Xa levels as a surrogate measure of efficacy and safety instead of clinical outcomes such as incidence of bleeding, VTE recurrence or mortality. One open-label retrospective study including 193 patients investigated the use of TBW for the calculation of VTE treatment doses of dalteparin and used major haemorrhage as the primary outcome measure (20). Despite the limitations of their method, the authors concluded that the bleeding rate associated with TBW dosing in patients with high body weight is comparable to that observed in other patient groups being treated with dalteparin.

Although the limited evidence suggests that the use of TBW is safe, it has been proposed by some experts that LBW is a more appropriate parameter to use for the calculation of treatment doses of LMWH in patients with high body weight because TBW does not take into account the clearance rate of these drugs in the patient group (6). The use of LBW for LMWH dose calculation in this patient population has been studied by Green and Duffull (21). They propose complex LBW calculations and twice or thrice daily dosing. This evidence is limited to pharmacodynamic studies using enoxaparin only in patients up to 160 kg (21). A conventional versus individualized dosing regimen was compared in a randomized, controlled, double blind trial by the same authors (22). The study included 122 patients, 11 of whom weighed 100 kg or more. Both arms used the same dosing regimen for patients weighing less than 100 kg. For patients weighing 100 kg and over, the use of TBW in the conventional arm was compared to the use of LBW. The authors concluded that the use of LBW resulted in a reduction of bleeding and major bruising in their overall patient sample, however, specific results for patients with high body weight are difficult to interpret given the small patient numbers.

Concerning dose capping, based on the potential overdosing for TBW-based therapeutic LMWH regimens in obese patients, dose capping is often applied in clinical practice (6,7). However, a recent review by the European Society of Cardiology (ESC) Working Group on Thrombosis on antithrombotic therapy and body mass concluded that, with enoxaparin, there is insufficient evidence that dose capping results in improved safety or efficacy compared with a TBW dosing regimen without capping in class 2 obesity (35-39.9 kg/m2) and recommend against dose capping (23). In class 3 obesity (>40 kg/m2) there is more uncertainty regarding dose capping and the ESC Working Group on Thrombosis advocate anti-Xa monitoring in this group (23).

In summary, it is accepted that both TBW and LBW can be used for dose calculation of LMWH in patients with high body weight. The use of TBW involves administration of large doses of LMWH whereas the use of LBW involves complex dose calculations. Evidence for each approach remains scarce. Generally, dose capping is not recommended but often occurs in clinical practice due to the potential for overdose using TBW-based therapeutic LMWH dosing.

**2. Frequency of dosing**

As mentioned previously, twice daily dosing of enoxaparin is recommended for the treatment of VTE in patients with obesity (1). Additionally, dalteparin can be administered twice daily in patients with an increased risk of bleeding (3). Tinzaparin is licensed for once daily dosing only (2).

The use of TBW for the calculation of LMWH treatment doses in patients with high body weight can result in the prescribing of very high individual daily doses. This raises safety concerns regarding the need to split doses to avoid excessive peaks in drug activity and injection site bruising.

The frequency of LMWH dosing for the initial treatment of VTE in the general population has been the subject of a review by the Cochrane Collaboration (24). The authors concluded that once daily treatment is as effective and safe as twice daily treatment with LMWH, however, there was no specific analysis of results for patients with high body weight.

Only one retrospective, open-label study of 21 patients was identified comparing the same treatment dose of dalteparin given to patients with high body weight as a single or twice daily split dose (16). The dose was calculated based on TBW. The findings suggest that twice daily dosing is more effective in producing anti-Xa activity within the target range, however, the small sample size of the study is a significant limitation. Following a large randomized, multicentre, partially blinded clinical trial, the Enoxaparin Clinical Trial Group reported that enoxaparin 1.5 mg/kg once daily and enoxaparin 1mg/kg twice daily were clinically equivalent in the treatment of venous thromboembolic disease, despite a statistically non-significant trend of increased VTE recurrence in obese patients treated with enoxaparin once a day (n=137; 7.3%) when compared to twice a day (n=146; 3.4%) (25). No reports regarding altered frequency of tinzaparin dosing were identified.

In summary, enoxaparin should be administered twice daily in patients of high body weight. Dalteparin can be administered twice daily in patients at risk of bleeding and anti-Xa monitoring should be considered to ensure therapeutic levels are achieved. Tinzaparin is licensed for once daily dosing only.

**3. Monitoring of anti-Xa levels**

NICE guidance recommends anticoagulation treatment with regular monitoring of therapeutic levels for people with proximal DVT or PE who weigh less than 50 kg or more than 120 kg to ensure effective anticoagulation (26). Additionally, the manufacturer of dalteparin states that monitoring of anti-Xa levels should be considered for specific patient populations such as those with morbid obesity (3). By contrast, The American Society of Hematology does not advise using anti-Xa concentration monitoring to guide LMWH dose adjustment due to the lack of correlation between supratherapeutic anti-Xa concentrations and bleeding (27).

It is generally recommended that, after two to three days of therapy, a peak anti-Xa level is checked 4 hours post LMWH dose (12). Local haematology departments should be consulted to advise on monitoring requirements, such as when to initiate monitoring and how frequently this is required, and the most suitable target range for anti-Xa activity due to small variations in laboratory techniques.

Despite reservations about how well anti-Xa levels relate to clinical outcomes, it remains the best parameter available to monitor the safety of LMWH use in ‘at risk’ patient groups (28, 29).

**4. Alternative dosing strategies**

There is substantially more evidence available regarding the safe use of enoxaparin in patients of high body weight when compared to other LMWHs. Most recent studies have focused on the need for dose capping and alternative dosing strategies.

Current therapeutic enoxaparin dosing is generally based on TBW and, as described earlier, a dose cap is often applied in clinical practice. To balance the risk of bleeding against the risk of thrombosis, alternative dosing strategies have been proposed. These involve the use of a lower weight-based initial dose of between 0.75 mg/kg and 0.85 mg/kg (30, 31). In the literature, there is much controversy regarding these lower dosing protocols. Results from a recent retrospective audit supported the strategy of weight-based dosing of enoxaparin in obesity with no maximum dose, with anti-Xa levels suggested for obese patients with clinical risk factors for bleeding (32). This study involved three groups: Group 1 had patients >100 kg who received a dose of 1 mg/kg twice daily; Group 2 had patients who weighed <100 kg and received a dose of 1 mg/kg twice daily; Group 3 had patients >100 kg who received an enoxaparin dose of < 1mg/kg twice daily. The authors found that median anti-Xa levels and distribution were not significantly different between patients who weighed >100 kg and patients who weighed <100 kg. Furthermore, this study also found that obese patients who received an enoxaparin dose < 1mg/kg had subtherapeutic anti- Xa levels more frequently. Conversely, another study concluded that traditional 1mg/kg twice daily dosing based on TBW may not be appropriate and suggests that a starting dose of 0.75-0.85 mg/kg twice daily should be considered (33). The authors recommend that anti-Xa monitoring is conducted for all obese patients prescribed enoxaparin, irrespective of the dose, due to the complex pharmacokinetics and pharmacodynamics in obesity and the large interpatient variability. A single randomized controlled trial (RCT) was found, which aimed to evaluate the treatment dose of enoxaparin in acutely ill morbidly obese patients. The study compared anti-Xa levels of patients receiving 1 mg/kg twice daily with those receiving a reduced dose of 0.8 mg/kg twice daily (34). The trial failed to show statistically significant differences between the two dosing strategies. However, there was a 12.4% difference in primary outcome, resulting in 89.3% of patients achieving a goal anti-Xa when initiated on 0.8 mg/kg. Although this finding was not statistically significant, it was suggested to be clinically relevant.

In summary, despite the general recommendation that dose capping should be avoided, alternative dose capping strategies are proposed in the literature. Results are contradictory and inconclusive. Further, larger-scale RCTs are required to explore these alternative dosing strategies.

## 5. Practicalities around safe prescribing and administration

If it is considered necessary to split the daily dose of LMWH, a risk assessment must be made to ensure that increasing the frequency of dosing does not impact on other aspects of patient treatment. For example, care must be taken to avoid giving LMWHs too close to any recent or planned spinal interventions (including spinal or epidural anaesthetics, removal of epidural catheters, lumbar punctures, etc) as this can result in serious adverse events (1-3, 35).

The complexity of dose calculations should also be taken into account and, where possible, clear dose banding advice should be produced to enable the use of pre-filled syringes (36). This may involve rounding doses up or down as necessary.

## Summary

Treatment of VTE in patients with high body weight constitutes a challenge in clinical practice. Adjustments in dose calculation may be necessary in certain circumstances and may justify the off-label use of LMWHs. This decision should be made following careful consideration of both the clinical and practical risks introduced by changing standard practice in the prescribing of LMWHs. Monitoring of anti-Xa levels is key to the safe use of these medicines in this patient group.

The lack of clear guidance within the product licenses and the published literature may require the development of local specialist advice to support the management of these patients. Such a guideline has been developed within NHS Greater Glasgow and Clyde (available on request). It should be noted that this guidance is based on local specialist consensus and describes off-label use of LMWHs.

Limitations

This guidance is for adult patients only and does not apply to pregnant women. The content of this document is based on limited clinical evidence and should only be used as a guide for dosing adjustments until further data are available. This is not a comprehensive review of all LMWHs and only includes information on enoxaparin, dalteparin and tinzaparin.

**References**

(1) Summary of Product Characteristics- Clexane® pre-filled syringes (Enoxaparin). Sanofi. Accessed <http://www.medicines.org.uk/emc/product/4499/smpc> on 04/06/2020 [Date of revision of the text 26/05/2020].

(2) Summary of Product Characteristics-Innohep Syringe 20,000 IU/ml Solution for injection in pre-filled syringe (Tinzaparin). Leo Laboratories Limited. Accessed <http://www.medicines.org.uk/emc/product/3631/smpc> on 04/06/2020 [Date of revision of the text 13/04/2020].

(3) Summary of Product Characteristics- Fragmin 18,000 IU/0.72ml solution for injection (Dalteparin). Pfizer Limited. Accessed <http://www.medicines.org.uk/emc/product/4243/smpc> on 04/06/2020 [Date of revision of the text 17/04/2020].

(4) Cheymol G. Effects of obesity on pharmacokinetics. Implications for drug therapy. Clin Pharmacokinet 2000; 39(3): 215-231.

(5) Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol 2004; 58 (2): 119-133.

(6) Barras MA, Kirkpatrick CMJ, Green B. Current dosing of low-molecular-weight heparins does not reflect licensed product labels: an international survey. Br J Clin Pharmacol 2010; 69 (5): 520-528.

(7) Thomson P, Brocklebank C, Semchuk W. Treatment dosing of low-molecular-weight heparins and the dose cap dilemma: considerations for patients in Canada. Can J Hosp Pharm 2009; 62(5): 367-374.

(8) Andrassy K, Eschenfelder V. Are the pharmacokinetic parameters of low molecular weight heparins predictive of their clinical efficacy? Thromb Res 1996; 81 (2S): S29-S38.

(9) Frydman A. Low-molecular-weight heparins: an overview of their pharmacodynamics, pharmacokinetics and metabolism in humans. Haemostasis 1996; 26 (suppl 2): 24-38.

(10) Ihaddadene R, Carrier M. The use of anticoagulants for the treatment and prevention of venous thromboembolism in obese patients: implications for safety. Expert Opin Drug Saf 2016; 15(1): 65-74.

(11) Messerli FH, Christie B, DeCarvalho JGR et al. Obesity and essential hypertension. Hemodynamics, intravascular volume, sodium excretion, and plasma renin activity. Arch Intern Med 1981; 141: 81-85.

(12) Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants. Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 2012; 141 (2) (Suppl): e24S-e43S.

(13) Nutescu EA, Spinler SA, Wittkowsky A, Dager WE. Low-molecular-weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother 2009; 43: 1064-1083.

(14) Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018; 2(22): 3198-3225.

(15) Sanderink G, Liboux A, Jariwala N et al. The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. Clin Pharmacol Ther 2002; 72: 308-318.

(16) Smith J, Canton EM. Weight-based administration of dalteparin in obese patients. Am J Health Syst Pharm 2003; 60: 683-687.

(17) Wilson S, Wilbur K, Burton E, Anderson DR . Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. Haemostasis 2001; 31: 42-48.

(18) Hainer JW, Barrett JS, Assaid CA et al. Dosing in heavy-weight/ obese patients with the LMWH tinzaparin: a pharmacodynamic study. Thromb Haemost 2002; 87: 817-823.

(19) Bazinet A, Almanric K, Brunet C et al. Dosage of enoxaparin among obese and renal impairment patients. Thromb Res 2005; 116: 41-50.

(20) Al-Yaseen E, Wells PS, Anderson J et al. The safety of dosing dalteparin based on actual body weight for the treatment of acute venous thromboembolism in obese patients. J Thromb Haemost 2005; 3: 100-102.

(21) Green B, Duffull SB. Development of a dosing strategy for enoxaparin in obese patients. Br J Clin Pharmacol 2003; 56: 96-103.

(22) Barras MA, Duffull SB, Atherton JJ et al. Individualized compared with conventional dosing of enoxaparin. Clin Pharmacol Ther 2008; 83(6): 882-888.

(23) Rocca B, Fox KAA, Ajjan RA et al. Antithrombotic therapy and body mass: An expert position paper of the ESC Working Group on Thrombosis. Eur Heart J. 2018; 39(19): 1672-1686.

(24) Bhutia S, Wong PF. Once versus twice daily low molecular weight heparin for the initial treatment of venous thromboembolism. Cochrane Database of Systematic Reviews 2013; issue 7. Art no. CD003074.

(25) Merli G, Spiro TE, Olsson CG et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med 2001; 134 (3): 191-202.

(26) National Institute for Health and Care Excellence. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. London: NICE; 2020 (Clinical guidelines [NG158]).

(27) Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018; 2(22): 3257-3291.

(28) Gouin-Thibault I, Pautas E, Siguret V. Safety profile of different low-molecular weight heparins used at therapeutic dose. Drug Saf. 2005; 28 (4): 333-349.

(29) Lim W. Using low molecular weight heparin in special patient populations. J Thromb Thrombolysis 2010; 29: 233-240.

(30) Deal EN, Hollands JM, Riney JN, Skrupky LP, Smith JR, Reichley RM. Evaluation of therapeutic anticoagulation with enoxaparin and associated anti-Xa monitoring in patients with morbid obesity: a case series. J Thromb Thrombolysis 2011; 32(2):188–194.

(31) Lalama JT, Feeney ME, Vandiver JW, Beavers KD, Walter LN, McClintic JR. Assessing an enoxaparin dosing protocol in morbidly obese patients. J Thromb Thrombolysis. 2015;39(4):516-521.

(32) Maclachlan KH, Stevens HP, Tran HA, Chunilal SD. Weight-Based Enoxaparin for Venous Thromboembolism in Obesity Gives Similar Anti-Xa Levels to Patients <100 kg, with No Increase in Major Bleeding. Semin Thromb Hemost. 2019. 45(1): 94-99.

(33) van Oosterom, N., Winckel, K. & Barras, M. Evaluation of weight based enoxaparin dosing on anti-Xa concentrations in patients with obesity. J Thromb Thrombolysis. 2019. 48**:** 387–393.

(34)Curry MA, LaFollette JA, Alexander BR, Evans KS, Tran RH, Kempton CL. Evaluation of Treatment-Dose Enoxaparin in Acutely Ill Morbidly Obese Patients at an Academic Medical Center: A Randomized Clinical Trial. Ann Pharmacother. 2019. 53(6): 567-573.

(35) NHS England. Harm from using low molecular weight heparins when contraindicated – Patient Safety Alert NHS/PSA/W/2015/001 [19th January 2015].

(36) NHS National Patient Safety Agency. Reducing treatment dose errors with low molecular weight heparins – NPSA Alert NPSA/2010/RRR014 [30th July 2010].

## Quality Assurance

### Prepared by

### Debbie Thomson, Medicines Information Pharmacist, NHS Greater Glasgow and Clyde

### Date Prepared

June 2020

Checked byMorven Henry, Medicines Information Pharmacist, NHS Greater Glasgow and Clyde

### Date of check

July 2020

### **Contac**t

medinfo@ggc.scot.nhs.uk

### Search strategy

1. Embase

:exp low molecular weright heparin/ AND exp pharmacokinetics/ and limit ‘2016- current’ AND exp obesity/

:exp low molecular weight heparin/ AND exp obesity/ and limit ‘2016-current’ AND exp thromboembolism

1. Medline

:exp Heparin, Low-Molecular-Weight/ AND exp pharmacokinetics/ AND [exp weight gain/ OR obesity /OR exp obesity, morbid] AND limit ‘2016-current’

:exp Heparin, Low-Molecular-Weight/ AND [exp weight gain/ OR obesity /OR exp obesity, morbid] AND limit ‘2016-current’

1. Electronic Medicines Compendium
2. Cochrane Library
3. Micromedex
4. Martindale
5. NHS Evidence
6. National Institute for Health and Care Excellence
7. Scottish Intercollegiate Guidelines Network
8. NHS National Patient Safety Agency and Department of health Central Alerting System
9. American College of chest physicians Clinical guidelines