How to optimise anticoagulation for patients who are obese

Abstract

Management of anticoagulation has become a hot topic in the last decade. Health-care professionals are encountering increasing number of patients diagnosed with a thromboembolic episode, probably as a result of heightened awareness. In addition, the recognition that hospital-acquired thrombosis causes substantial mortality has led to an emphasis on appropriate thromboprophylaxis in all patients deemed at risk of thrombosis. However, the use of anticoagulants for both treatment and prophylaxis of thrombosis can pose a challenge in individuals who are obese. There are no detailed studies in this area and as such the dosing and monitoring of anticoagulants in these individuals can be problematic.

Key words: Obesity; Anticoagulation; Morbidly obese; Venous thromboembolism prophylaxis; Venous thromboembolism treatment.

Submitted: 9 October 2019; accepted following double blind peer review: 17 October 2019

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Introduction

The prevalence of obesity has nearly tripled in the last three decades according to World Health Organization data, with over 650 million adults being classified as obese in 2016 (NCD Risk Factor Collaboration, 2017). One of the well-recognised complications of obesity is venous thromboembolism, which includes both deep vein thrombosis and pulmonary embolism. However, prophylaxis and treatment of venous thromboembolism in patients who are obese is challenging because of the lack of high-quality data in this patient population. This review addresses and summarises current evidence for prophylaxis for venous thromboembolism and treatment in patients who are obese, suggesting a pragmatic approach in the medical, surgical and obstetric setting.

Obesity is defined as having an excessive fat accumulation that may impair health with a body mass index of ≥30 kg/m^2. Those patients who have a body mass index of ≥40 kg/m^2 are categorised as 'morbidly obese'. Several studies have shown that individuals who are obese have an increased risk of venous thromboembolism. In a meta-analysis of one cohort study and eight case-control studies, Ageno et al (2008) found that individuals who were obese were twice as likely to have a venous thromboembolism compared to individuals with a normal body mass index (odds ratio=2.33; 95% confidence interval=1.68–2.34). After excluding four studies that were of low quality or had inadequate body mass index recordings, obesity was found to be associated with an increased risk of venous thromboembolism (odds ratio of 1.84; 95% confidence interval=1.55–2.18). In a multivariate analysis, Steffen and colleagues (2009) found obesity to be associated with a similar risk for developing venous thromboembolism in men (odds ratio=2.31, 95% confidence interval=1.48–3.62) and women (odds ratio=1.84, 95% confidence interval=1.19–2.84).

The literature has demonstrated a linear relationship between body mass index and risk of venous thromboembolism (Eichinger et al, 2008; Kabrhel et al, 2009; Severinsen et al, 2009). One prospective cohort study which involved 87 226 women found that, after accounting for other risk factors for venous thromboembolism such as previous surgeries and cancer, the relative risk of unprovoked pulmonary embolism increased by about 8% per 1 kg/m^2 (Kabrhel et al, 2009). The risk of pulmonary embolism was found to be increased nearly sixfold in those individuals with a body mass index of ≥35 kg/m^2 (Kabrhel et al, 2009). Similarly, Severinsen and colleagues (2009) found increasing odds ratio of venous thromboembolism among men and women with increasing body mass index.

How to cite this article:
Raja H, Thachil J. How to optimise anticoagulation for patients who are obese. Br J Hosp Med. 2020;81(1):1–8. https://doi.org/10.12968/hmed.2019.0323

Pathophysiology of the enhanced risk of venous thromboembolism in patients who are obese

Obesity is widely recognised as a prothrombotic state in both men and women. Several mechanisms have been proposed to explain this association (Figure 1) (Blokhin and Lentz, 2013). Fibrinolysis, a key physiological process that results in the degradation of the fibrin clot by plasmin, is impaired in individuals who are obese through increased production of plasminogen activator inhibitor-1 from adipocytes and hepatocytes (Shimomura et al, 1996; Ouchi et al, 2011). These cellular changes are driven by increased levels of circulating free fatty acids. Another major mechanism is the promotion of a chronic inflammatory state that activates prothrombotic signalling pathways in vascular cells and induces platelet activity (Levi et al, 2012).

It is likely that amplification of such mechanisms in patients with larger body mass index may be linked to the increased incidence of venous thromboembolism. In addition, patients who are obese are more likely to experience longer periods of immobility and to have poor gait, as well as being more likely to have co-existing diseases such as diabetes and osteoarthritis (Pi-Sunyer, 2009). These factors may further impair venous return from the lower limbs and thus lead to a greater risk of venous thromboembolism.

Prophylaxis of venous thromboembolism in patients who are obese

When prescribing prophylaxis for venous thromboembolism, clinicians often face a dilemma between increasing the dose of anticoagulant in line with increasing body weight or capping the dose to prevent unwanted toxicity such as major haemorrhage. Making these decisions based on the little available evidence has led to several studies being conducted in this area.

Medical patients

A prospective study by Tahaineh et al (2018) evaluated the degree of anticoagulation achieved in patients who are obese or morbidly obese receiving enoxaparin for prophylaxis for venous thromboembolism. They found that 88.5% of patients (n=23) who received enoxaparin for prophylaxis were on a fixed daily dose of 40 mg; only 44% of this group (n=10) achieved the target therapeutic anti-factor Xa level (Tahaineh et al, 2018). These data are in keeping with earlier studies which suggested that other factors besides patients' body mass index are responsible for achieving therapeutic anti-factor Xa levels (Malinoski et al, 2010; Costantini et al, 2013). Despite this finding, no adverse thrombotic or bleeding events were identified in those with a subtherapeutic or supratherapeutic anti-factor Xa level respectively.

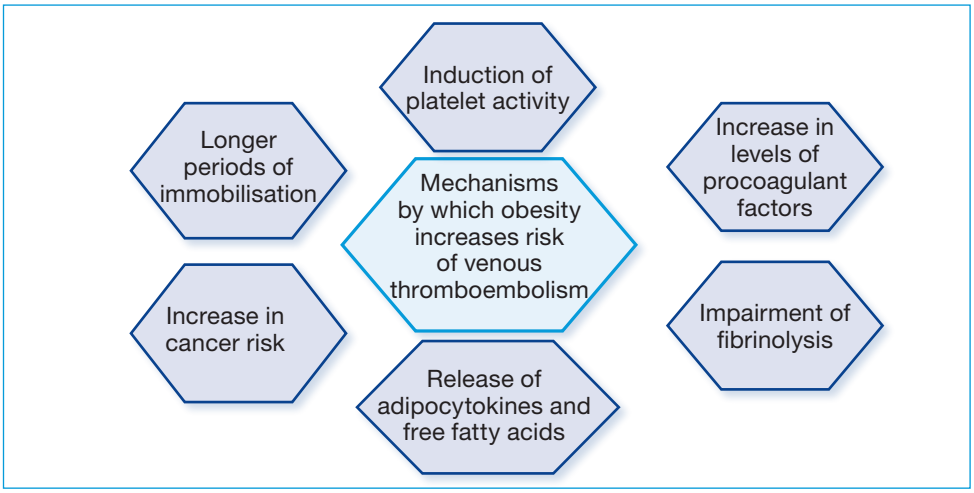

Figure 1. Proposed thrombotic mechanisms in obesity. The release of adipocytokines and free fatty acids is reported to play a key role in causing inflammation and endothelial dysfunction which can lead to thrombus formation. Importantly, the rise in risk of venous thromboembolism in individuals who are obese is most likely attributable to a dynamic interplay between these factors.

In a retrospective study of 3928 patients who were morbidly obese, Wang et al (2014) compared the incidence of venous thromboembolism in patients who received high-dose thromboprophylaxis (heparin 7500 units three times daily or enoxaparin 40 mg twice daily) to those who received standard doses (heparin 5000 units two or three times daily or enoxaparin 40 mg once daily). High-dose thromboprophylaxis halved the odds of in-hospital venous thromboembolism in inpatients who were morbidly obese (odds ratio=0.52; 95% confidence interval=0.27–1.00, *P*=0.05) (Wang et al, 2014). Importantly, the study found no increase in bleeding risk for those on high-dose thromboprophylaxis (odds ratio 0.84, 95% confidence interval=0.66–1.07, *P*=0.15) (Wang et al, 2014). Similarly, when implementing a weight-based prophylactic regimen of enoxaparin 0.5 mg/kg daily in 28 inpatients who were morbidly obese, Rondina et al (2010) found no bleeding events or symptomatic venous thromboembolism. The authors also reported that most patients achieved anti-factor Xa levels within or near the recommended range for thromboprophylaxis (Rondina et al, 2010).

As the incidence of venous thromboembolism rises in line with the obesity epidemic, clinicians are increasingly facing the problem of what is the most appropriate prophylaxis for venous thromboembolism for medical patients with a body mass index ≥40 kg/m^2. Based on current evidence, the authors recommend that patients who are obese need a higher dose or dosing frequency to match drug exposure to that of the non-obese population. Close monitoring of anti-factor Xa levels, with peak levels checked at 4 hours post-dose (after the third dose), is also recommended to ensure drug optimisation and avoid potentially harmful effects of drug accumulation. Owing to a lack of high quality studies, however, there is uncertainty about what dose to use and whether to choose a weight-based dose-adjustment or fixed-dose strategy for thromboprophylaxis in patients who are morbidly obese. The authors' practice is outlined in **Figure 2**.

Surgical patients

Obese patients who undergo surgery are at a high risk of developing venous thromboembolism, with incidence rates persisting for up to 3 months post-surgery. Implementing prophylaxis for venous thromboembolism is therefore an important aspect of surgical care, particularly in high-risk groups such as patients who are obese.

Dosing for prophylaxis for venous thromboembolism in surgical patients who are obese has been guided largely by data from the general surgery and bariatric literature (Freeman et al, 2010). In a prospective open trial, Borkgren-Okonek et al (2008) demonstrated the safety and efficacy of a body mass index-stratified enoxaparin thromboprophylaxis regimen in 223 patients undergoing gastric bypass surgery. Patients received enoxaparin 40 mg twice daily (body mass index 35–50 kg/m^2, *n*=124) or 60 mg twice daily (body mass index of >50 kg/m^2, *n*=99), and once daily for 10 days post-discharge. The authors found that 79%

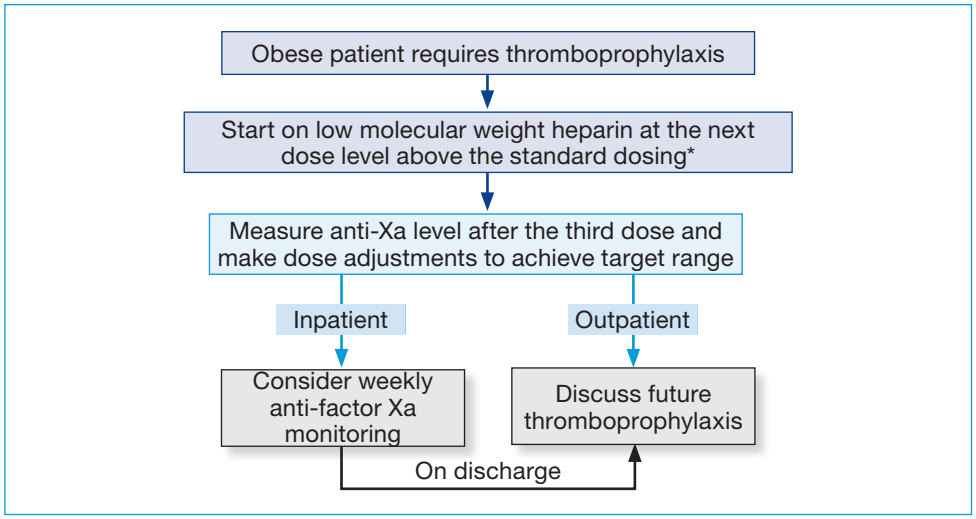

Figure 2. Recommended treatment for venous thromboembolism prophylaxis in patients who are obese. The asterisk denotes that the dose may be the next level above the standard dose for patients who are not obese, for example, 7500 units of dalteparin instead of 5000 units.

of patients had reached a target anti-factor Xa level (0.2–0.4 units/ml), bleeding rates were low (1.79%) and venous thromboembolism occurred in only one patient (0.45%) (Borkgren-Okonek et al, 2008). A similar study by Singh et al (2012) found that body mass index-based preoperative dosing of low molecular weight heparin along with postoperative prophylaxis was both safe and effective in patients who were obese undergoing Roux-en-Y gastric bypass surgery (n=170).

Scholten and colleagues (2002) assessed two enoxaparin regimens (30 or 40 mg twice daily) in 481 patients undergoing bariatric surgery. The authors found fewer venous thromboemboli in the 40 mg twice-daily group compared to the 30 mg twice-daily group (0.6% *vs* 5.4%, P<0.01) (Scholten et al, 2002). It is worth noting, however, that this finding may have been influenced by the shorter operative times and inpatient stays in the former group. Importantly, it highlights the need for investigators to design more robust randomised controlled studies to remove such sources of potential bias. More recently, Venclauskas et al (2018) conducted a systematic review on perioperative prophylaxis for venous thromboembolism in surgical patients who are obese. The authors recommended that patients who are morbidly obese should receive higher doses of anticoagulants than patients who are obese to ensure adequate prophylactic effect (Venclauskas et al, 2018).

The optimal dosing strategies for thromboprophylaxis in surgical patients who are obese are yet to be elucidated. There are promising data on offering post-discharge prophylaxis to these patients and so this should be considered (Aminian et al, 2017). The duration of prophylaxis should be tailored depending on procedure-related risk factors for venous thromboembolism in surgery such as operative time, type of procedure, and whether an open or laparoscopic approach is used. Further evaluation of these parameters in trials is warranted to better guide decision making on dosing and duration of prophylaxis for venous thromboembolism in this cohort of patients. Clinicians should actively encourage patients who are obese to lose weight before elective procedures to improve venous thromboembolism outcomes.

Obstetrics

Managing prophylaxis for venous thromboembolism for women who are obese within the obstetric setting can pose a different issue for clinicians. Pregnancy alone increases the risk of venous thromboembolism five to tenfold compared to that in non-pregnant women (Bates et al, 2016). The postpartum period carries a higher risk with the likelihood of developing a venous thromboembolism being greatest in the first 3–6 weeks after delivery (Bates et al, 2016). Pregnant women who are obese are therefore likely to have a substantially higher risk of a venous thromboembolism. Having a better understanding of the management of venous thromboembolism in these patients is important because, although the rate of obstetric venous thromboembolism events remains low, they are a significant cause of maternal morbidity and mortality worldwide (Bates et al, 2016).

The preferred agent for prophylaxis for venous thromboembolism during pregnancy is heparin because, unlike vitamin K antagonists such as warfarin, this does not cross the placenta to adversely affect fetal development and health. It is also safe and easy to use, and is the agent of choice for the postpartum period. Low molecular weight heparins offer several advantages over unfractionated heparins, including better efficacy and lower risk of bleeding and heparin-induced thrombocytopenia (Warkentin et al, 1995; Romualdi et al, 2013). If contraindications exist for heparin, then clinicians may consider heparinoids such as fondaparinux following discussion with haematology.

At present, there is disparity in the way that venous thromboembolism is managed in pregnant women who are obese because of a lack of high-quality research being available to guide appropriate dosing of low molecular weight heparins. The Royal College of Obstetricians and Gynaecologists (2015) has suggested daily doses for dalteparin, enoxaparin and tinzaparin to provide some guidance in this area, albeit without any level 1 evidence.

A recent systematic review by Hellgren and Mistafa (2019) concluded that dalteparin resulted in a low risk of venous thromboembolism recurrence in pregnant women. The authors highlighted the need to increase the dose of low molecular weight heparin as the pregnancy progresses in order to accommodate for physiological changes such as increased weight gain, increased renal clearance of low molecular weight heparin, and higher glomerular filtration rate (Hellgren and Mistafa, 2019). Although this review analysed

a variety of dosing regimens and did not include studies focusing on pregnant women who were obese, the authors suggest that a weight-based dosing regimen is prudent for dalteparin and other low molecular weight heparins, unless the bleeding risk in a specific situation is excessive.

Treatment for venous thromboembolism in patients who are obese

Establishing a patient on treatment for venous thromboembolism requires an initial phase of high-dose low molecular weight heparin followed with long-term warfarin or a direct oral anticoagulant such as oral direct thrombin inhibitors and anti-factor Xa inhibitors (Figure 3). The decision to select either warfarin or a direct oral anticoagulant can be challenging in patients who are obese because of a paucity of well-conducted studies. Consideration of clinical factors, such as ease of reversibility, and patient preferences is key to this process.

Medical and surgical patients

A retrospective study by Tellor et al (2018) evaluated the impact of body mass index on warfarin requirements in two separate groups (n=585 and n=379 respectively). The authors found that patients who are morbidly obese required a greater total weekly dose than normal or underweight patients to maintain a therapeutic international normalised ratio (41.5 mg vs 28.8 mg, P<0.05, and 41 mg vs 24.4 mg, P=0.021 respectively) (Tellor et al, 2018). Similarly, Wallace et al (2013) demonstrated that patients who were obese required higher doses of warfarin to achieve the desired target international normalised ratio compared to patients who were not obese. Deal et al (2011) conducted a retrospective case series of 26 patients who were morbidly obese who received enoxaparin at a therapeutic dose of 0.8 mg/kg every 12 hours. No bleeding events occurred in the 12 patients (46%) who achieved the target anti-factor Xa level, but of the 10 patients with a high anti-factor Xa level, four had a bleeding event (Deal et al, 2011). More recently, a retrospective study of 102 patients showed that weight-based dosing of enoxaparin at 1 mg/kg twice daily with no maximum dose was effective for reaching therapeutic anti-factor Xa levels in patients who were obese and being treated for a venous thromboembolism. This dosing regimen was not associated with an increased risk of major bleeding (Maclachlan et al, 2019).

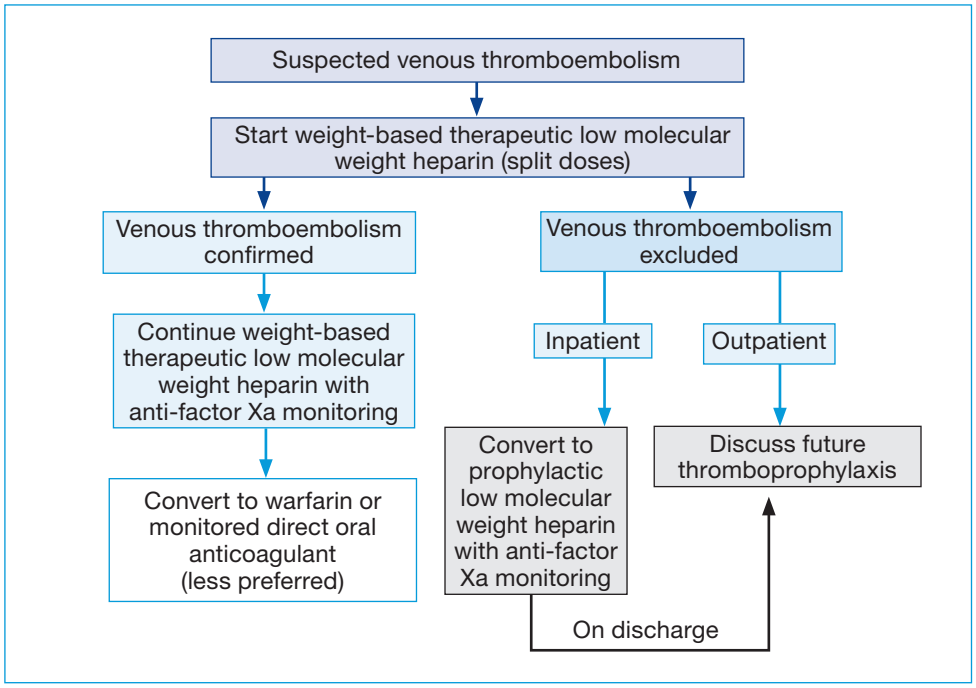

Figure 3. Recommended treatment for a patient who is obese and is suspected to have a venous thromboembolism.

The role of direct oral anticoagulants

In 2016, the International Society on Thrombosis and Haemostasis recommended avoiding use of direct oral anticoagulants in patients who are morbidly obese or those with a weight of >120 kg unless drug levels were closely monitored (Martin et al, 2016). Reasons for this were the paucity of relevant data in this population group and concerns about under-dosing. Since the International Society on Thrombosis and Haemostasis guidance document, several trials have explored the role of direct oral anticoagulants in patients who are morbidly obese (Di Nisio et al, 2016; Kido and Ngorsuraches, 2019). Drawing solid conclusions from these trials is challenging because of their study designs. For example, Di Nisio and colleagues (2016) reported that rivaroxaban showed no association between body mass index and risk of recurrent venous thromboembolism or clinically relevant bleeding; but all patients who were extremely obese were grouped into ≥100 kg or body mass index ≥35 kg/m^2, limiting the strengths of their conclusion. In a retrospective study focusing on a small group of patients who were morbidly obese with atrial fibrillation or flutter (n=128), Kido and Ngorsuraches (2019) found that apixaban and rivaroxaban had a similar efficacy and safety profile as warfarin. The authors also highlighted the need to be cautious with dabigatran because of the higher rates of stroke or transient ischaemic attack.

At present, the authors recommend using warfarin or a direct oral anticoagulant to treat a venous thromboembolism in patients with a body mass index of <40 kg/m^2. For patients with a body mass index of ≥40 kg/m^2, it would be prudent to use only warfarin until further robust clinical data become available to support definitive prescribing of a direct oral anticoagulant. If a direct oral anticoagulant is preferred by the patient, then drug levels should be monitored to ensure adequacy of dosing (Martin et al, 2016).

Obstetrics

Management of acute venous thromboembolism in pregnant women who are obese warrants careful evaluation of the clinical situation. Timely medical intervention with treatment-dose low molecular weight heparin or unfractionated heparin is often needed to ensure safety of the patient and fetus. As discussed earlier, physiological parameters in pregnancy can alter the pharmacokinetic properties of heparins. Dosing of low molecular weight heparin for pregnant patients who are obese should therefore be weight-based. The option to proceed with a once-daily or twice-daily dosing regimen is at the discretion of the prescribing clinician.

Conclusions

Patients who are obese are no longer exceptional in clinical practice. The incidence of obesity will continue to rise in the foreseeable future which in turn will lead to increased morbidity and mortality from thrombotic disorders. This growing sub-group of patients, however, are largely under-represented in or excluded from trials assessing the management of venous thromboembolism. This prevents definite conclusions being drawn about the most effective and safe options for prophylaxis and treatment of venous thromboembolism in patients who are obese. This review summarises the best available evidence for the management of venous thromboembolism in three different obese patient groups: medical, surgical and obstetric. Randomised controlled trials are urgently needed to compare methods for managing venous thromboembolism in patients who are obese. In particular, investigators should design more robust trials that separate patients who are obese from those who are morbidly obese using the World Health Organization body mass index criteria to enable international standardisation. This, in turn, will provide greater reassurance to prescribing clinicians.

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Conflicts of interest

The authors declare no conflicts of interest.

Key points

- Rising rates of obesity worldwide are leading to more venous thromboembolism events.
- Several mechanisms contribute to increasing thrombotic risk in patients who are obese.
- Owing to a lack of high-quality data, disparity exists in venous thromboembolism treatment and thromboprophylaxis in patients who are obese, with a wide variety of dosing and treatment regimens being used in clinical practice.
- Patients who are morbidly obese are underrepresented in research and, therefore, require better inclusion going forward.
- Randomized controlled trials are urgently needed to find the optimal venous thromboembolism prophylactic and treatment regimens for patients who are obese and those who are morbidly obese.

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