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RECOMMENDATIONS

Unresolved questions on venous thromboembolic disease. Venous thromboembolism (VTE) management in obese patients. Consensus statement of the French Society of Vascular Medicine (SFMV)

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Summary Obesity is an alarming worldwide public health issue and is defined as a body mass index (BMI) of 30 kg/m^2 or more. It is considered as a risk factor for first thrombotic event and is associated with a significant risk of recurrence. Consequently, obese patients are often treated by anticoagulant therapy but data from randomised control trial are scarce. We will review in this narrative review the state of the art of the prescription of anticoagulant for the prevention and treatment of venous thromboembolism (VTE) in obese patients.
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Introduction

Obesity is a worldwide public health issue and is defined as a body mass index (BMI) of 30 kg/m^2 and above. There are three classes of obesity as defined by Centers for Disease Control and Prevention (CDC): class 1: BMI of 30 to < 35, class 2: BMI of 35 to < 40 and class 3: BMI of 40 or higher [1]. It is considered as a risk factor for first thrombotic event and it is associated with a significant risk of recurrence [2,3]. Consequently, obese patients are often treated by anticoagulant therapy but data from randomised control trial are scarce. We will review the state of the art of the prescription

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of anticoagulant for the treatment and secondary prevention of venous thromboembolism (VTE) in obese patients and for VTE prevention after bariatric surgery and prevention in medicine.

Treatments of venous thromboembolism in obese patients

Low molecular weight heparin (LMWH)

Cap or uncap the dose?

Monography of dalteparin and tinzaparin suggest capping the dose to a maximum of 18,000 international units (IU) subcuteanous (SC) daily, due to the absence of data, while there is no capping recommendation for enoxaparin. In the RIETE register, the retrospective observational data showed that obese patients receiving capped doses of LMWH (18,000 IU/day) had significantly lower rates of composite events (recurrent VTE, major bleeding, or all-cause death attributable to LMWH). However, the groups receiving capped or uncapped dose were not similar and a higher rate of major bleeding in the uncapped dosing group mainly drove the results [4]. A small clinical study has suggested that up to 190 kg, safety and efficacy of dalteparin was not different in obese versus non-obese patients treated with uncapped weight adjusted LMWH [3]. More recently, a review of existing data has concluded that capping was not justified and dose calculation should be based on the current body weight [3,5,6]. These conclusions are supported by pharmacokinetics and small clinical studies of enoxaparin, tinzaparin [7,8] and dalteparin[3]. Of note, Wave study is a Canadian single group pilot ongoing trial which aims to demonstrate the safety of weight adjusted dosage of LMWH in the management of cancer associated VTE in obese patients [9].

Anti-Xa monitoring?

LMWH have a pharmacokinetic profile allowing for weight-based dosing without the need for routine laboratory monitoring [3]. However, extremely obese patients studies have shown that over 150 kg the rate of supratherapeutic patients increased on enoxaparin [10]. Of note in this study, the enoxaparin anti-Xa range was between 0.5 to 1.1 UI/mL, which is below the expected range of enoxaparin, and therefore leading to many patients in the supratherapeutic range. With tinzaparin, a recent small study showed that tinzaparin treatment dosed per actual body weight does not lead to an overdose or accumulation in hospitalized medical patients [8]. No obvious linear correlation was found between BMI and anti-Xa level which makes dose effect relation difficult to anticipate [8] and other authors have shown that the anti-Xa concentration are not strongly associated with either thrombosis or bleeding events [11].

Other drawback of anti-Xa monitoring is the lack of standardization dosing methods and its reproducibility [12,13].

Based on these elements of weak correlations with bleeding or thrombosis, and concerns over standardisation and reproducibility, American Society of Hematology 2018 guidelines [14] suggest not to monitor anti-Xa to adjust LMWH doses, as well as Smythe et al. [15].

Although generally not recommended, it could be considered to monitor anti Xa activity to detect supratherapeutic anti-Xa level in patients with BMI > 40 (> 190 kg) those with severe renal impairment, and those with moderate renal impairment with prolonged anticoagulation (> 10 days) [5,16].

Once daily or twice daily injections?

A discrepancy between the different LMWHs available is the number of injections. Tinzaparin and dalteparin are delivered in one daily injection at 175 and 200 IU/kg/day, respectively. Maximum dose by injection is 18,000 IU, which requires 2 injections in obese patient. Whether or not these injections should be performed at the same time is unknown but two injections at the same time would be more consistent with the once-daily injection in non-obese patients. Enoxaparin is available in 1 or 2 daily injections at 150 IU/kg/d and 100 IU/kg/12 h respectively. In Merli et al. study that was not specifically designed with obese patients, enoxaparin seemed to be more effective in a twice daily injection with risk of failure by 2.9% compared to 4.4% with once daily injection but this difference was not significant [17].

Fondaparinux

Fondaparinux is a synthetic pentasaccharide. Unlike the LMWH Phase 3 trials, the MATISSE trials included a relatively high proportion of morbidly obese and obese patients leading to consider this treatment as an alternative. Thus, a once daily injection of fondaparinux was adjusted to patient body weight (5 mg if < 50 kg, 7.5 mg if 50—100 kg and 10 mg if > 100 kg) [18]. Incidence of recurrences or major bleeding were similar in fondaparinux compared to heparin treatment group [19,20].

Direct oral anticoagulants

Xaban: apixaban, rivaroxaban

Pharmacokinetic/pharmacodynamic modeling (PK/PD) studies provide information but must be taken with caution given the absence of correlation between plasma level and clinical outcome. In agreement with other studies, a recent prospective pharmacokinetic study from our group showed that among 146 obese patients, treated with DOAC (rivaroxaban and apixaban), 124 (85%) had DOAC concentrations similar to those of non-obese patients and, 2 (1%) patients developed recurrent thrombosis during 16.4 (0.4—132) months follow-up with DOAC concentrations in the expected range [21].

No specific prospective studies on obese patients are available and most data come from health care system from US or registries. Rivaroxaban compared to warfarin in obese patients was associated with a lower rate of recurrence with no safety difference and no statistical difference was found across BMI categories for either recurrent VTE or bleeding complications [22—25]. Data from RCT Einstein DVT ant PE found no difference in recurrent VTE in patients with warfarin [26], also effective and safe on patients with patients BMI > 40 regardless of the severity of the thromboembolic event (intermediate or high risk PE) [27].

Similarly, recent data from the healthcare system has provided information about apixaban. In 23,344 obese

patients and 19,751 morbidly obese patients, the safety and efficacy of apixaban compared to warfarin was similar of non-obese patients [28]. In a recent review and meta-analysis, Xabans were shown to have lower odds of major bleeding but similar odds of recurrent VTE when compared with VKAs in treating VTE in morbidly obese patients. Large registry analyses or future randomized controlled trials will be helpful in confirming these findings [29].

A subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) has updated the 2016 recommendations based on the results of phase IV studies. The experts suggest that the use of direct oral anticoagulants (DOACs) is feasible regardless of patients' weight or body mass index (BMI) [30].

Dose reduction

In secondary prophylaxis after a first VTE, Einstein choice and Amplify-ext trials have demonstrated that a dose reduction for rivaroxaban and apixaban, respectively, was better than low dose aspirin or placebo to prevent recurrence. In these studies, efficacy and safety outcome in obese patients were lacking. Furthermore, whether a dose reduction improves the benefit risk balance is still under research [31]. ISTH subcommittee do not recommend a dose reduction in obese patients [30].

Long-term curative anticoagulation in the setting of bariatric surgery

Bariatric surgery is a challenge because it potentially affects the absorption of oral anticoagulants such as vitamin K antagonists (VKAs) and DOACs. The main bariatrics procedures are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), biliopancreatic diversion with duodenal switch (BPD-DS) and gastric banding (GB). SG and GB result in weight loss through restriction of caloric intake while RYGB and BPD-DS also induce a degree of malabsorption [32]. Warfarin is absorbed in the proximal part of digestive tract (stomach, duodenum, and jejunum). Clinical studies have shown reduced dose requirements within the 1 to 3 months after surgery and then normalization or toward increased warfarin dose requirements compared to pre surgery dose intake. Apixaban is potentially absorbed in the stomach, duodenum, and jejunum and rivaroxaban in stomach and duodenum [32]. A recent study, which compared anti-Xa levels (peaks, through, AUC, half life) before surgery and 1, 6, 12 months after surgery after a single dose of apixaban, has demonstrated a reduction of the AUC 1 year after the surgery and of the 3 hours post-dose anti-level Xa [33]. Another study based on 18 patients on apixaban showed that post-op anti-Xa levels were in the therapeutic range and were not different than before the surgery [34]. In the same study, anti-Xa level while on rivaroxaban tended to decrease after RYGB. A recent study involving 102 patients with a median follow-up of 187 days (IQR: 82.5—627.5) demonstrated that the use of apixaban or rivaroxaban after bariatric surgery in the context of treatment for venous thromboembolism (VTE) or secondary prevention did not result in a significant thrombotic or hemorrhagic risk increase [35].

ISTH experts have suggested to distinguish 2 periods of treatment after bariatric surgery [30]:

- within the 1st month: there are concerns about absorption of DOAC and INR lability on warfarin, parenteral anticoagulant such as LMWH is the anticoagulant of choice;
- after the 1st month: an oral switch is suggested to VKA or DOAC. If DOAC is chosen, prescribers should check the absorption with anti Xa peak and through level. However, there are no clinically validated therapeutic range with DOAC.

Thromboprophylaxis in obese patients

Weight adjustment for thromboembolism prophylaxis for medical patients

Optimal dosage of anticoagulant is unknown, due to lack of strong clinical evidence [16]. In the setting of medically ill patients, various approaches are used, one consists on the weight adjusted dose of enoxaparin at 0.5 mg/kg once daily [36]. Other authors suggest enoxaparin to be used at 4000 IU every 12 h. For dalteparin and patient with BMI < 40, it is suggested to not adjust the dose [37].

Weight adjusted tinzaparin is associated with low risk of bleeding and VTE event for prophylaxis of patients with BMI > 30 kg/m^2 at 50 UI/kg; or for patients weighing $\geq$ 160 kg, with 50 UI/kg or 75 UI/kg [38,39].

Post-surgery/bariatric surgery

Though large randomized trials are missing, various possibilities are offered to the clinician; literature usually mentions either a fixed dosed of either 3000 IU or 4000 IU every 12 h, [40,41] or a dose adapted to weight 50 IU/kg/day [42], though, a meta-analysis points the low evidence of the efficacy of higher dosage (> 4000 UI or 3000 UI every 12 h) [43].

Practice survey shows a very large variability on the anticoagulation dose used by surgeon ranging from 4000 UI daily to dose mass index adjustments [44]. European guidelines 2018 of the European Society of Anesthesiology [45] define various anticoagulation options with the patients risk class. High risk patients are defined as having either or > 55 years, BMI > 55 kg/m^2, history of VTE, venous disease, sleep apnoea, hypercoagulability and pulmonary hypertension. They suggest a prophylactic dose for bariatric surgery of LMWH (3000 to 4000 anti-Xa IU every 12 h), depending on BMI, as acceptable for obese patients with a lower risk of VTE (grade 2B), and suggest the use of a higher dose of LMWH (4000 to 6000 anti-Xa IU every 12 h) as acceptable for obese patients with a higher risk of VTE (Grade 2B). They suggest using only anti coagulants or intermittent pneumatic compression (IPC) for obese patients with a low risk of VTE during and after bariatric procedures (grade 2C). They recommend using anticoagulants and IPC together for obese patients with a high risk of VTE during and after bariatric procedures (grade 1C).

For non-bariatric surgery, they suggest to consider for patients with BMI > 40, LMWH dose of 3000 to 4000 anti-Xa IU every 12 h (Table 1).

[1] No data available over 222 kg (75 kg/m^2).

Table 1 Suggested doses of anticoagulant in adult patient with BMI > 30.

VTE treatment	Type	Suggested dose	Notes	Dosage
	Fondaparinux	10 mg once daily		
	Enoxaparin	100 IU/kg q12 h	Uncapped	
	Tinzaparin	175 IU/kg once daily	Uncapped	
	Apixaban	10 mg q12 h for a week then 5 mg q12 h		
	Rivaroxaban	15 mg q12 h for 21 days then 20 mg daily		
	Dalteparin	200 IU/kg once daily first month 150 IU/kg once daily after first month	Uncapped	
	VKA	Adjusted with INR		
VTE treatment after Bariatric surgery	If DOAC, after 4 weeks of LMWH			Through concentration measurement
VTE prophylaxis in medicine	Enoxaparin	4000 IU q12 h		
VTE prophylaxis post bariatric surgery	Enoxaparin	3000—4000 IU q12 h hours		Platelets counts 2/w for 3 weeks then once a week
VTE prophylaxis in non-bariatric surgery	Enoxaparin	4000 IU daily Consider 3000—4000 IU q 12 h hours if BMI > 40		

In obese patient on long-term anticoagulant for treatment of acute VTE and secondary prophylaxis of VTE, we suggest:

- an uncapped dosing regimen for LMWH unless contraindicated[1];
- the monitoring of anti-Xa activity in patients with BMI > 40 kg/m^2, or with renal impairment, and treated with uncapped LMWH could be considered to avoid supratherapeutic dosage or to detect accumulation;
- that 10 mg of fondaparinux is an alternative in patient without severe renal insufficiency (ClCr < 30 mL/min);
- DOAC without monitoring or warfarin unless contraindicated;
- to avoid dose reduction of DOAC in secondary prophylaxis.

In obese patient treated by bariatric surgery, we suggest:

- parenteral anticoagulant in the early phase after bariatric surgery for a minimum of 4 weeks, with platelets monitoring twice a week for 3 weeks then once a week;
- prescribing VKA or DOAC in long-term secondary prophylaxis of VTE after bariatric surgery. If DOAC switch is needed, after 4 weeks of LMWH, we recommend to monitor through anti-Xa level and through DOAC concentration to verify the drug absorption.

Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

CRediT authorship contribution statement

S. Miranda: writing original draft, I. Gouin-Thibault, M. Talbot, B. Espinasse, G. Mahe: visualization, writing review & editing.

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