Anticoagulation in obese patients: challenges and strategies

Alice Lipari,[1,2] Esmeralda Capristo,[2,3] Antonietta Ferretti,[4] Erica De Candia[2,4]

[1]Department of Internal Medicine, Azienda Ospedaliera San Camillo-Forlanini, Rome; [2]Department of Translational Medicine and Surgery, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome; [3]Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome; [4]Department of Laboratory and Hematological Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

ABSTRACT

Obesity is a chronic complex disease, related to several comorbidities, including cardiovascular diseases, insulin resistance, and venous thromboembolism (VTE). Its rising prevalence, especially among individuals with extreme obesity, poses several management challenges, particularly with regard to anticoagulant therapy. The pharmacokinetics and pharmacodynamics of anticoagulants are altered in obese patients, requiring tailored therapeutic strategies. This review examines the challenges faced when managing anticoagulation in obese individuals, focusing on both parenteral and oral anticoagulants. Obesity influences drug absorption, distribution, metabolism, and elimination, complicating the use of both parenteral agents like low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), and fondaparinux and oral agents, such as vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). Oral anticoagulant administration represents a great challenge also in patients who undergo bariatric surgery, which further impacts on drug bioavailability by modifying gastrointestinal anatomy. In general, data on the efficacy and safety of DOACs in severely obese individuals, particularly those who have undergone bariatric surgery, remain limited. This review highlights the importance of individualized anticoagulation approaches, especially for high-risk patients, and highlights the need for further research to establish appropriate management strategies for the population of obese patients. Such studies are crucial to improve the safety and efficacy of anticoagulant therapy in this growing population.

Correspondence: Erica De Candia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS Largo Agostino Gemelli 8, 00136 Rome, Italy.
E-mail: erica.decandia@unicatt.it

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Introduction

Obesity is a chronic complex disease, characterized by excessive fat deposits, due to an imbalance of energy intake and energy expenditure. Its prevalence is 13% in the global population, accounting for 650 million worldwide.[1] The diagnosis of overweight and obesity is made calculating the body mass index (BMI), that is weight (expressed in kilograms) divided by height squared (expressed in meters). In adults overweight is defined as a BMI greater than or equal to 25 kg/m^2, and obesity as a BMI greater than or equal to 30 kg/m^2.

Adipose tissue function and deposition, though, differ by sex. Males, in fact, tend to accrue more visceral fat, leading to the classic android body shape, whereas females accrue more fat in the subcutaneous depot prior to menopause; after menopause, fat deposition and accrual shift to favor the visceral depot. In particular, premenopausal women tend to store fat on the hips, thighs and buttocks, by contrast men accumulate fat predominately in the abdominal region.[2]

There are different ways to analyze fat distribution and body composition, such as bioelectrical impedance analysis (BIA), bioelectrical impedance spectroscopy (BIS), skinfold measurement (SKF), air/water displacement plethysmography. Besides being the gold standard for bone mineral density measurements, dual-energy x-ray absorptiometry (DEXA) is also used to estimate total and regional body fat and lean tissue mass, precisely estimating the relative mass of bone, lean tissue and total and regional fat, by way of the differential attenuation of x-rays when passing through each.[3]

It is well known that obesity, and in particular abdominal obesity, influences the effects of insulin on peripheral glucose and

fatty acid utilization, often causing type 2 diabetes mellitus. This condition, characterized by insulin resistance and, consequently hyperinsulinemia and hyperglycemia, leads to vascular endothelial dysfunction and inflammation, altered lipid metabolism and hypertension, which all are promoters of atherosclerotic cardiovascular disease.[4-6]. Individuals with obesity are three times more likely to develop type 2 diabetes mellitus than normal weight individuals and weight loss interventions can positively affect glycemic control, including remission to a non-diabetic status.[7]

Long-time obesity, especially childhood obesity, is also associated with alterations in cardiac structure and function, including increased left ventricular mass and increased left ventricular and left atrial diameter, greater epicardial fat, and systolic and diastolic dysfunction.[8,9]

Overweight and obese people are also more likely to develop hypertension than normal weight individuals.[7,10] Indeed, visceral fat accumulation is strongly associated with hypertension development, as increase blood volume and fluid retention, especially in the adipose tissue, increases blood venous return and cardiac output.[7]

It is therefore not unusual that obese individuals develop cardiovascular diseases, such as atrial fibrillation (AF) or ischemic heart disease, at an early age. Indeed, obesity and overweight are associated with an increased risk of developing recurrent atrial arrhythmias after AF ablation.[11] Obesity is also one of the most relevant risk factors for venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), among hospitalized and out-patients. High BMI, indeed, has been consistently associated with elevated risk of VTE, and the risk increases with an increase in BMI, in a linear proportion.[12-15]

This condition might be due to different predisposing conditions, such as venous stasis, elevated concentrations of hemostatic and inflammatory biomarkers and increased risk of other diseases known to increase the risk of VTE, such as cancer.[14] Obesity is indeed a recognized risk factor for the development of postmenopausal breast cancer, as well as cancers of the colon, endometrium, kidney, esophagus, pancreas, liver, and gallbladder. Moreover, it is associated with increased cancer-related mortality.[16]

As obesity becomes more and more common, the prevalence of obese patients who require anticoagulant therapy, both to prevent cardioembolic stroke events in AF and to prevent VTE or VTE progression[11,17] increases. Indeed, management of anticoagulant therapy in the obese population is often tough, as there are different pharmacokinetic and pharmacodynamic characteristics that influence treatment outcomes. In fact, obesity significantly alters drug absorption, distribution, metabolism, and elimination, especially with regard to parenteral anticoagulants, which are absorbed subcutaneously.[18]

In fact, pharmacokinetics of the low-molecular-weight heparin (LMWH) enoxaparin is different in obese individuals, as it results in a markedly larger volume of distribution in obese compared to nonobese individuals. Hence, steady state exposure is achieved later and time to maximum anti-Xa activity is 1-hour longer in these patients.[19]

These findings highlight the need for tailored anticoagulation strategies in order to guarantee safety efficacy in managing thromboembolic risk. For this reason, finding a suitable therapy for this special group of patients is challenging, as they are often excluded from major clinical trials and clinical evidence about this category of patients is based for the most part on secondary and post-hoc studies.

Oral anticoagulation

The choice of an oral anticoagulant therapy for obese patients should consider the differences of intestinal absorption, metabolization and elimination of anticoagulant drugs in this population, with a specific further complication represented by bariatric surgery.

To this regard, surgery aimed at obtaining loss of weight includes many different techniques that provide restriction of gastro-intestinal volumes, intestinal hormone alterations, and malabsorption of nutritive substances, with the intention to affect satiety, macronutrients absorption, and insulin sensitivity.[20] These procedures can be distinguished in three main categories: restrictive procedures, malabsorptive procedures, and techniques that combine both restriction and malabsorption.[20]

Restrictive procedures aim at reducing caloric intake by reducing the stomach's reservoir capacity; the most well-known and used nowadays is sleeve gastrectomy, which is probably more successful than the other restrictive procedures because of its hormonal effects on hunger control. Other restrictive procedures are intragastric balloon placement or aspiration therapy, however they produce a more gradual and modest weight loss and subjects often relapse into pathological obesity.[20]

Malabsorptive procedures, such as jejunoileal bypass and biliopancreatic diversion, deeply modify gastrointestinal anatomy, decreasing the effectiveness of nutrient absorption by way of reducing the absorption length of the functional small intestine. They all lead to a massive weight loss, however they can also cause important metabolic complications, such as severe malnutrition, electrolyte imbalance and micronutrient deficiency.[20-22]

Lastly, procedures such as Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch and single-anastomosis duodenal ileal bypass with sleeve gastrectomy (SADI-S) are both restrictive and malabsorptive.[20-22]

All these procedures, performed with the aim of reducing the absorption of nutritional substances, also reduce absorption of drugs and medications, including oral anticoagulants.[23] Bariatric surgery can affect the bioavailability of oral anticoagulants in many ways. In particular, restrictive procedures, which reduce gastric volumes, may alter drug absorption as it is influenced by food ingestion, especially for rivaroxaban, and modify gastric pH; malabsorptive procedures, on the other hand, might exclude major sites of drug absorption, such as duodenum and proximal jejunum, and alter gastrointestinal transit time.[24-28]

For this reason, it is crucial to gather information on the specific bariatric surgery performed on the patient to choose the best anticoagulant according to the missing gastrointestinal absorptive portion.

Vitamin K anticoagulants

Warfarin and other vitamin K anticoagulants (VKAs) have been available for many years and are still used in different settings. Since direct oral anticoagulants (DOACs) became available in the last 15 years, VKAs use has significantly decreased. Main

reasons are their narrow therapeutic range due to influences many factors, such as genetic variation, drug and food interactions, and the need of continuous monitoring by INR measuring. In addition, bleeding risk, especially of intracranial hemorrhages, is higher with warfarin than with direct oral anticoagulants (DOACs).[11,17]

However, VKAs remain the drugs of choice in many situations, including prosthetic heart valves, antiphospholipid syndrome, end-stage renal failure or valvular AF.[11]

Unfortunately, patients with high BMI are largely underrepresented in the major clinical trials, and most recommendations come from *post-hoc* analyses of the main registration trials comparing DOACs *versus* AVK. For this reason, a real benefit in using DOAC versus VKAs in these patients has not been documented yet.

Interestingly, although obesity is related to an increased risk of developing AF, possibly due to electro-structural modulation of the atria,[29] *post-hoc* analysis of outcomes in obese patients in registration trials showed that they seem to present a decreased risk of stroke compared to normal weight patients (Table 1).[30-32] These findings, known as the "obesity paradox", are not completely understood. One hypothesis is that these patients undergo earlier and more intensive and aggressive treatments to manage cardiovascular risk factors. This phenomenon may also reveal lack of complete understanding of the complex pathophysiology of obesity and of the association between adiposity and cardiovascular diseases.[31]

Furthermore, some of these studies showed that VKA treatment is associated with a decreased risk of stroke and cardioembolic events compared to DOAC treatment in patients with high BMIs.[30,31,33] This phenomenon could be partially explained by a better time within the therapeutic range (TTR) in the group of obese patients as compared with TTR of normal weight patients in these studies. Though, findings coming from *post-hoc* analyses have several limitations.[30]

In contrast to the above reported studies, data obtained from the large ARISTOTLE trial documented that the superiority of efficacy and safety outcomes of apixaban compared with warfarin persists even in high weight patients.[32] Similar findings have been reported by a single health care observational study, which documented that patients with high BMI receiving DOACs had a decreased risk of cardio-embolic or bleeding events compared to patients with high BMI receiving warfarin, possibly associated with a less compliance of VKAs or with more inconsistent TTR, contrary to what shown by previous studies.[34]

However, the *post-hoc* ENGAGE AF-TIMI 48 trial also documented a higher risk of bleeding in obese patients, as the BMI increased, compared to normal weight patients, despite good control of INR in the VKAs group and no difference in DOACs

Table 1. DOACs *vs* VKAs efficacy and safety in patients with high BMI.

	Weight	Patients (n)		Efficacy (event rate per 100 patient/years) OR number of events (n OR %)	Major bleeding rate
Balla *et al.*[30]	BMI 18.5-24.9 kg/m^2	3289	Rivaroxaban=1618 VKA=1671	2.93 (n=166)[#]	3.69 (n=179)[#]
	BMI 25-29.9 kg/m^2	5535	Rivaroxaban=2738 VKA=797	2.28 (n=266)[#]	3.62 (n=314)[#]
	BMI ≥30 kg/m^2	5206	Rivaroxaban=2657 VKA=2549	1.88 (n=179)[#]	3.33 (n=279)[#]
Boriani *et al.*[31]	BMI 18.5 ≤25 kg/m^2	4491	Edoxaban=2933 VKA=1558	n=193 (6.58%) n=80 (5.13%)	n=157 (5.35%) n=126 (8.08%)
	BMI 25 ≤30 kg/m^2	7903	Edoxaban=5974 VKA=2629	n=262 (4.38%) n=145 (5.51%)	n=264 (4.41%) n=208 (7.91%)
	BMI 30 ≤35 kg/m^2	5209	Edoxaban=3506 VKA=1703	n=137 (3.91%) n=83 (4.87%)	n=188 (5.36%) n=130 (7.36%)
	BMI 35-40 kg/m^2	2099	Edoxaban=1413 VKA=686	n=52 (3.68%) n=18 (2.62%)	n=76 (5.37%) n=54 (7.87%)
	BMI ≥40 kg kg/m^2	1149	Edoxaban=785 VKA=364	n=21 (2.67%) n=5 (1.37%)	n=43 (5.47%) n=30 (8.24%)
Hohnloser *et al.*[32]	60-120 kg	15.172	Apixaban* VKA*	1.23 (n=73) 1.44 (n=201)	2.15 (n=277) 3.02 (n=379)
	>120 kg	982	Apixaban* VKA*	0.44 (n=4) 1.13 (n=11)	1.55 (n=13) 2.08 (n=19)
Malik *et al.*[33]	BMI >30 kg/m^2	*	DOACs* VKA*	5.8% 5.5%	5.5% 5.8%
Barakat *et al.*[34]	BMI 18.5 ≤30 kg/m^2	18.339	DOACs=8969 VKA=9370	2.66 6.02	4.20 9.10
	BMI 30 ≤40 kg/m^2	13.376	DOACs=7059 VKA=6317	2.35 4.90	3.81 8.88
	BMI ≥40 kg kg/m^2	3924	DOACs=2170 VKA=1754	1.70 3.64	3.22 8.10

DOAC, direct oral anticoagulants; VKA, vitamin K antagonist; *data not available; [#]individual data comparing efficacy and safety of VKA and rivaroxaban not available.

plasma concentrations or anti-Factor Xa activity.[31] The above discrepancy was attributed to a putative difference of pharmacodynamics and pharmacokinetics of anticoagulant drugs, which could affect their safety profile in high BMI patients (Table 1).

VKAs may also represent a reasonable choice over DOACs for stroke risk reduction and VTE treatment and prophylaxis in patients who underwent bariatric surgery.[28,35] Indeed, in these patients, pharmacokinetics, efficacy and safety of DOACs are still under investigation, whereas INR monitoring allows easy dose adjustments to ensure that patients remain in the desired therapeutic range.[28]

Direct oral anticoagulants

DOACs seem to be the best option for treatment of VTE and prevention of stroke in the general population of patients with AF, as they have demonstrated at least non-inferior efficacy compared with warfarin for the prevention of thromboembolism and they added benefit of 50% reduction in intracranial hemorrhage (ICH).[11,17]

Available DOACs include three direct inhibitor of factor Xa (FXa), such as rivaroxaban, apixaban and edoxaban, and one direct inhibitor of thrombin (FIIa), named dabigatran.

In 2021 a systematic review of the International Society on Thrombosis and Haemostasis (ISTH) recommended the use of DOACs for individuals with BMI up to 40 kg/m^2 or weight up to 120 kg.[23,36] Though, data analyzing DOACs individually in patients with high BMIs are limited.

A few studies reported data on the use of apixaban in obese patients. A small single-center, retrospective study showed that VTE recurrence, cardioembolic stroke and major bleeding events in patients with BMI ³40 kg/m^2 and with BMI ³50 kg/m^2 were similar in the group treated with apixaban and in the group treated with warfarin.[37] Another observational study showed a lower risk of recurrent VTE and of major bleeding in obese patients on apixaban compared to those on warfarin.[38] Pharmacokinetics studies showed modest or no effect of increased body weight on apixaban anti-Xa plasma levels. Overall, these findings indicate that standard dosing of apixaban seem to have similar effectiveness and safety for AF and VTE treatment in patients with obesity.[39-43]

The use of rivaroxaban in obese patients has been analyzed in a post hoc analysis of the EINSTEIN trials, which found no significant difference of VTE recurrency in patients under rivaroxaban compared to those under warfarin.[44] Several observational studies focused on the use of rivaroxaban *versus* warfarin for VTE recurrency in obese patients and documented similar efficacy and bleeding outcomes of the two treatments.[28,45-47] High-body weight population seem to present similar rates of stroke when treated with either rivaroxaban or warfarin for AF.[46] In addition, pharmacokinetics profile of rivaroxaban does not seem to be affected by increased body weight.[42,43,48-50] Thus, standard dosing of rivaroxaban seems to be effective and safe for both VTE and AF patients with morbid obesity.[42]

Dabigatran administered to patients weighing >100 Kg in the RE-LY trial resulted in lower trough drug concentrations, but similar peak drug concentrations compared to the reference body weight group.[51] Another study, including only 10 patients taking dabigatran for all indications, showed lower peak drug plasma concentration in patients weighing >120 kg.[52] A few more studies focused on the use of dabigatran in obese patients with atrial fibrillation showed that dabigatran was as effective as warfarin in these patients. However, these studies reported possible increased risk of gastrointestinal bleeding in obese patients, thus suggesting caution for its use in this category of patients.[53-55]

A recent study, investigating the plasma through and peak concentration of DOACs in obese patients, showed that dabigatran was associated with higher risk of trough and peak plasma concentrations below expected ranges. On the contrary, apixaban was associated with a lower risk of below-range drug level. This result could be partly explained by the higher proportion of patients with an obesity class ³ II in the dabigatran group. Another likely hypothesis might be the different dabigatran bioavailability in these patients. considering that it is the only DOAC administered as a pro-drug and needs to be activated.[56]

With regard to edoxaban, a *post-hoc* analysis of ENGAGE AF-TIMI 48 trial showed similar trough edoxaban concentration and anti-Xa activity among groups with different BMI ranging from 18.5 to >40 kg/m^2.[31] As far as we know, standard dosing of edoxaban should be effective and safe for stroke prevention in patients with AF and morbid obesity.[42].

There are no studies, to the best of our knowledge, investigating the effectiveness of dabigatran and edoxaban for treatment or prevention of VTE in morbidly obese patients. For this reason, in contrast to AF, they should be cautiously avoided in this clinical context (Table 2).[36,42,43]

The ISTH do not recommend measuring peak and trough DOAC levels, as there are still insufficient data to influence management decisions and no specific and therapeutic ranges of drug have been defined.[36] However, recent data indicate that measuring plasma levels of DOACs may have a role in the management of anticoagulation in the general population and in obese patients.

Very recent data showed a correlation between low and high trough DOAC levels and the risk of thrombotic and bleeding

Table 2. Guidance statements for DOACs use in patients with obesity.

DOAC	BMI ≤40 kg/m^2 or weight ≤120 kg	BMI >40 kg/m^2 or weight >120 kg		
		AF*	VTE treatment#	VTE prevention#
Rivaroxaban	Suggested	Suggested (standard doses)	Suggested (standard doses)	Suggested (standard doses)°
Apixaban	Suggested	Suggested (standard doses)	Suggested (standard doses)	Suggested (standard doses)°
Edoxaban	Suggested	Suggested (standard doses)	Not suggested[2]	Not suggested[§]
Dabigatran	Suggested	Suggested (standard doses)	Not suggested[3]	Not suggested[$]

DOAC, direct oral anticoagulants; *Steffel *et al.*[43]; #Martin *et al.*[36]; °drug approval restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness; [§]lack of clinical and pharmacokinetics/pharmacodynamics data; [$]unconvincing data.

events, respectively, in general non obese patients.[57,58] Moreover, a very recent paper reported that patients with obesity and AF have high risk of having below-range trough and peak plasma concentrations of DOACs.[56]

Further data in the future are needed to indicate whether measuring plasma levels in obese patients might help managing direct oral anticoagulants in these special patients.

There is also insufficient evidence available with regard to which DOAC dose is indicated for obese patients during the extended treatment of VTE after the initial 6 months of full dose.[36] Another open topic is prevention of VTE in obese patients who need bariatric surgery. ISTH suggests to not use DOAC for treatment and prevention of VTE in the acute setting right after surgery. Instead, ISTH suggests administering at least 4 weeks of parenteral treatment followed by oral anticoagulants, with the support of DOAC trough and peak levels to check for drug absorption and bioavailability, when possible.[36] The fear of absorption after bariatric surgery is the main concern which may limit the use of DOAC in this context.[11,17]

Apixaban is usually absorbed primarily by the upper gastrointestinal tract, and, to a small extent, by colon and by the distal small bowel.[43] For this reason, only RYGB surgery seems to partially affect apixaban absorption, whereas restrictive and malabsorptive procedures do not.[36] Rivaroxaban is absorbed mainly in the stomach, and, in small quantities, in the small intestine; so, the drug absorption is possibly reduced by both restrictive and absorptive bariatric procedures.[36,43] Edoxaban is assimilated by the proximal small intestine, but requires acid environment for a correct absorption. Dabigatran is absorbed by the lower part of the stomach and the proximal part of the small intestine.[36,43] Hence, also edoxaban and dabigatran absorption is affected by both restrictive and absorptive bariatric procedures (Table 3).

Published data on this topic are scarce and provide conflicting results. A single-center study reported that bariatric surgeries, and in particular sleeve gastrectomy and RYGB, do not seem to modify pharmacokinetics of rivaroxaban 10 mg administered as post-bariatric antithrombotic prophylaxis.[59] However, whether the pharmacokinetics parameters remain unaltered over the whole period of weight loss is unknown, as the rivaroxaban levels were measured only few days after bariatric surgery.[59] On the contrary, another study showed that patients who underwent sleeve gastrectomy had subtherapeutic peak plasma levels of rivaroxaban 15 mg and 20 mg, whereas peak plasma levels of apixaban 5 mg and dabigatran 110 mg and 150 mg were within the expected range[60]. Despite demonstration of adequate dabigatran peak plasma levels in obese patients after sleeve gastrectomy, data on the efficacy and safety of dabigatran in individuals with a high BMI are limited. Therefore, dabigatran is recommended in patients with BMI ≤40 kg/m^2 or weight <120 kg, but not for patients with BMI >40 kg/m^2 or weight>120 kg (Table 2).[36]

The studies published so far on this topic have great limitations, i.e., the exiguity of the sample size, the variety of DOACs and different types of bariatric surgery reported, thus they do not provide definitive information.[60]

One study reported the clinical outcomes in post-bariatric surgery patients treated with apixaban (n=42) and rivaroxaban (n=60) for VTE. Overall incidence of VTE recurrence was low, with no recurrence in the apixaban group and 1 recurrency in the rivaroxaban group. No major bleeding was reported in the apixaban group, whereas 5% of patients in the rivaroxaban group had major bleedings.[28] Hence, apixaban seems to show the best safety/efficacy profile for VTE treatment in these patients, especially when it is not used in the immediate postoperative period. Currently it is suggested to choose a parenteral anticoagulant for the first few weeks after surgery followed by switching to a DOAC with the help of trough plasma level measurement of the chosen drug for optimization of antithrombotic therapy.[28,36]

Parenteral anticoagulation

Heparin is an endogenous polysaccharide, with of anticoagulant, anti-inflammatory, and antiangiogenic effects.[61,62] The form of heparin that is used clinically as an anticoagulant is obtained from porcine or bovine intestinal mucosa.[63]

Heparin exert its anticoagulant action indirectly, by binding to antithrombin (AT). This bond leads to a conformational change in AT, which turns from a slow to a rapid inactivator of coagulation factors.[64]

Unfractionated heparin (UFH) is metabolized in the reticuloendothelial system and in the liver, and it is excreted in the urine; therefore, its elimination is not affected by kidney function. LMWH is obtained from enzymatic or chemical depolymerization of UFH and it is metabolized in the liver and excreted by the kidney;[65,66] for this reason, patients with impaired kidney function generally require dose adjustment or use of an alternative anticoagulant drug.[63]

Unfractioned heparin

The onset of intravenous UFH is immediate, whereas peak plasma levels of subcutaneous UFH is reached in two-four hours.[63]

Table 3. Absorption of DOACs in patients who underwent bariatric surgery.

DOAC	Sites of absorption	Restrictive procedures (*e.g.*, sleeve gastrectomy)	Malabsorptive procedures (*e.g.*, jejunoileal bypass)	Combined restrictive and malabsorptive procedures (*e.g.*, RYGB)
Apixaban	Upper GI tractColonDistal small bowel	Unlikely affected	Unlikely affected	Possibly affected
Rivaroxaban	StomachSmall bowel	Possibly affected	Possibly affected	Possibly affected
Edoxaban	Proximal small bowel	Possibly affected	Possibly affected	Possibly affected
Dabigatran	StomachProximal small bowel	Possibly affected	Possibly affected	Possibly affected

DOAC, direct oral anticoagulants; RYGB, Roux-en-Y gastric bypass; GI, gastrointestinal.

Although UFH requires frequent laboratory monitoring to achieve and maintain therapeutic levels, based on the aPTT, it is the drug of choice in patients with severe kidney impairment, with high risk of bleeding, and in patients candidate for surgical procedures. It is also a reasonable choice in patients whose poor subcutaneous absorption is suspected, such as obesity. UFH can be administered intravenously with two different therapeutic schemes: a fixed protocol or a weight-based protocol.

The fixed protocol requires an initial intravenous bolus of 5000 IU followed by a heparin dose of 40.000 IU as a 24-hour continuous infusion. The weight-based protocol includes an initial intravenous bolus of 80 IU/Kg (with a maximum dose of 10.000 IU), followed by a continuous intravenous infusion at an initial rate of 18 IU/kg/hour (with a maximum dose of 2.000 IU/hour).[63]

In both protocols heparin dose should be adjusted using the aPTT, which is performed approximately four-six hours after administration.

Low molecular weight heparin

LMWH is usually administered subcutaneously with plasma peak levels three to five hours after administration, while steady state levels are normally reached after two to three days of therapy.[67]

However, subcutaneous absorption of LMWH can be markedly affected by the distribution of adipose tissue in obese patients. Variations in subcutaneous adipose tissue composition between obese and normal-weight population can lead to altered pharmacokinetics, resulting in delayed absorption and inconsistent prophylactic or therapeutic drug levels. Indeed, increased adipose tissue may hinder drug's penetration and absorption from the injection site, potentially necessitating adjustments in dosing protocols to achieve optimal anticoagulation.[68-70]

There are different types of available LMWH, such as enoxaparin, dalteparin, tinzaparin and nadroparin. They are all administered subcutaneously in fixed or weight-based dosing without monitoring. In individuals with a high BMI, data on optimal dosing are uncertain.

Concerning VTE prophylaxis, in 2012 the American College of Chest Physicians suggested weight- based prophylactic dosing compared to fixed dosing.[71] By contrast in 2018 and in 2019 the American Society of Hematology did not provide a specific preference between the use of weight-based or fixed doses of LMWH.[72,73]

In 2021 a meta-analysis reported similar efficacy and safety of LMWH regardless of the dosing approach.[74]

In particular, enoxaparin is recommended at standard prophylaxis dosing (i.e., 30 mg every 12 h or 40 mg once daily) in patients with BMI between 30 and 39 kg/m^2, although some clinicians use weight-based dosing (i.e., 0.5 mg/kg once or twice daily, depending upon level of VTE risk) as it is usually administered in patients with BMI ≥40 kg/m^2 (i.e., 0.5 mg/kg once or twice daily).[71,75-79] In the bariatric surgery scenario, it is suggested that in patients with high VTE-risk with BMI ≤50 kg/m^2 it is administered LMWH at a dosage of 40 mg every 12 h,[80,81] whilst in patients with BMI >50 kg/m^2 at a dosage of 60 mg every 12 h (Table 4).[81]

For tinzaparin, in patients with BMI between 30 and 39 kg/m^2 it is suggested to use standard fixed prophylaxis dosing (i.e., 3500 or 4500 IU), whereas in patients with orthopedic surgery it is suggested to use a weight-based prophylaxis dosing (i.e., 50 or 75 IU/kg).[75] As tinzaparin safety and efficacy has not been fully determined, it is recommended clinical and laboratory monitoring when using this drug.[82]

Regarding VTE treatment, enoxaparin is usually administered at standard treatment dosing (i.e., 1 mg/kg every 12 h), as once-daily administration is not recommended. Likewise, tinzaparin is used at standard treatment dosing, as well (i.e., 175 UI/kg once daily) (Table 4).[75]

Unfortunately, studies regarding therapeutic intensity of LMWH in patients with high BMI all are underpowered. To achieve an optimal anticoagulation, clinicians can be helped by anti-factor Xa levels monitoring, which can be crucial for optimizing LMWH therapy in obese individuals, but especially in high-risk hospitalized obese patients.[70] Anti-factor Xa levels should be measured approximately three to five hours after a dose and after at least two doses. Anti-factor Xa levels are not routinely used, as no specific therapeutic and prophylactic ranges are defined, but in such situations could represent a reasonable choice.

Although a clear clinical relevance of anti-factor Xa levels has not been determined yet[83] in obese patients who need appropriate anticoagulant therapy measurement of anti-F Xa plasma levels might help to manage targeted adjusted therapies.

Fondaparinux

Fondaparinux consists of a penthasaccaride sequence, which is the smallest unit of heparin able to bind to and to induce the conformational change of antithrombin. Fondaparinux binds to AT with a higher affinity than UFH or LMWH and induces efficacious inactivation of factor Xa.[84,85]

Fondaparinux is given subcutaneously once daily, and it is to-

Table 4. Suggested doses of subcutaneous enoxaparin in adult patients with high BMI and normal kidney function.

	BMI 30 to 39 kg/m^2	BMI 40 ≥ kg/m^2	High VTE-risk bariatric surgery with BMI ≤50 kg/m^2	High VTE-risk bariatric surgery with BMI >50 kg/m^2
VTE treatment	**Standard treatment dosing (*i.e.*, 1 mg/kg every 12 h based on total body weight)**			
VTE prophylaxis	30 mg every 12 h OR 40 mg every 24 h	Empirically increase by 30% the following: 30 mg every 12 h OR 40 mg every 24 h	40 mg every 12 h	60 mg every 12 h

BMI, body mass index; VTE, venous thromboembolism; conversion: 1 mg of enoxaparin is approximately equal to 100 IU of enoxaparin.

tally available after subcutaneous injection.[84,85] Its peak serum concentrations are reached in about 2 h later and it is finally cleared by kidneys and excreted in the urine.[86] One advantage of fondaparinux is that heparin-induced thrombocytopenia (HIT) is very unlikely, as there are very rare cases reported in the literature.[87,88]

In individuals with normal renal function the dose depends on body weight, in particular for patients weighing >100 kg it is recommended to administrate fondaparinux 10 mg once daily for VTE treatment, whereas for VTE prophylaxis it might be used fondaparinux 2.5 mg. Unfortunately, there are no recommendations on how to manage patients with very high BMI. In order to overcome this problem, it is suggested to measure anti-factor Xa activity approximately three hours after the dose of drug is administered. The therapeutic range has not been established yet, but usually levels are in the range of 0.39-0.5 µg/mL for prophylactic dose and 0.5-1.5 µg/mL for therapeutic dose.[75-77]

How I treat

The management of anticoagulant therapy in morbidly obese patients may be very challenging. To our knowledge and experience, the best option is a patient-tailored approach, considering drug bioavailability, fat distribution and altered gastrointestinal anatomy. We highlight that the following suggestions are only partially supported by evidence available, though they represent reasonable choices based on current knowledge. In patients who underwent bariatric surgery it is crucial to figure out which specific procedure has been performed, in order to choose the most appropriate oral anticoagulant.

In general, we prefer not to use DOACs in patients with combined restrictive and malabsorptive bariatric procedures and we tend to prefer apixaban over the other DOACs in patients who underwent restrictive and malabsorptive only procedures, as they unlikely affect absorption of apixaban.

In patients with morbid obesity who require an anticoagulant therapy for AF or for treatment or prevention of VTE, in whom pharmacokinetics and pharmacodynamics are uncertain, we suggest measuring peak and trough specific DOAC levels, when available. When DOAC levels are not in therapeutic ranges, it is reasonable to switch into another anticoagulant.

When DOAC levels cannot be measured, in patients with very high BMI or in patients who underwent surgery, which had greatly altered the gastrointestinal anatomy, VKAs seem to represent an effective and safe choice of therapy (Figure 1).

With regards to parenteral anticoagulation, LMWH is the most commonly used type of drug in our clinical practice, but its dosing is often difficult to manage in patients with high BMI.

It is important to remember, especially in patients who require a rapid achievement of optimal therapeutic levels (i.e., treatment of extended and proximal deep vein thrombosis or pulmonary embolism), that subcutaneous administration may lead to a late achievement of the steady state exposure. In these situations, intravenous UFH could represent a reasonable choice although dose adjusting to obtain a therapeutic range requires frequent laboratory monitoring.

In our opinion it is also essential to consider subcutaneous fat distribution, as in patients with a greater abdominal adipose panniculus administration of LMWH in another subcutaneous site should be preferred, in order to avoid delayed drug absorption.

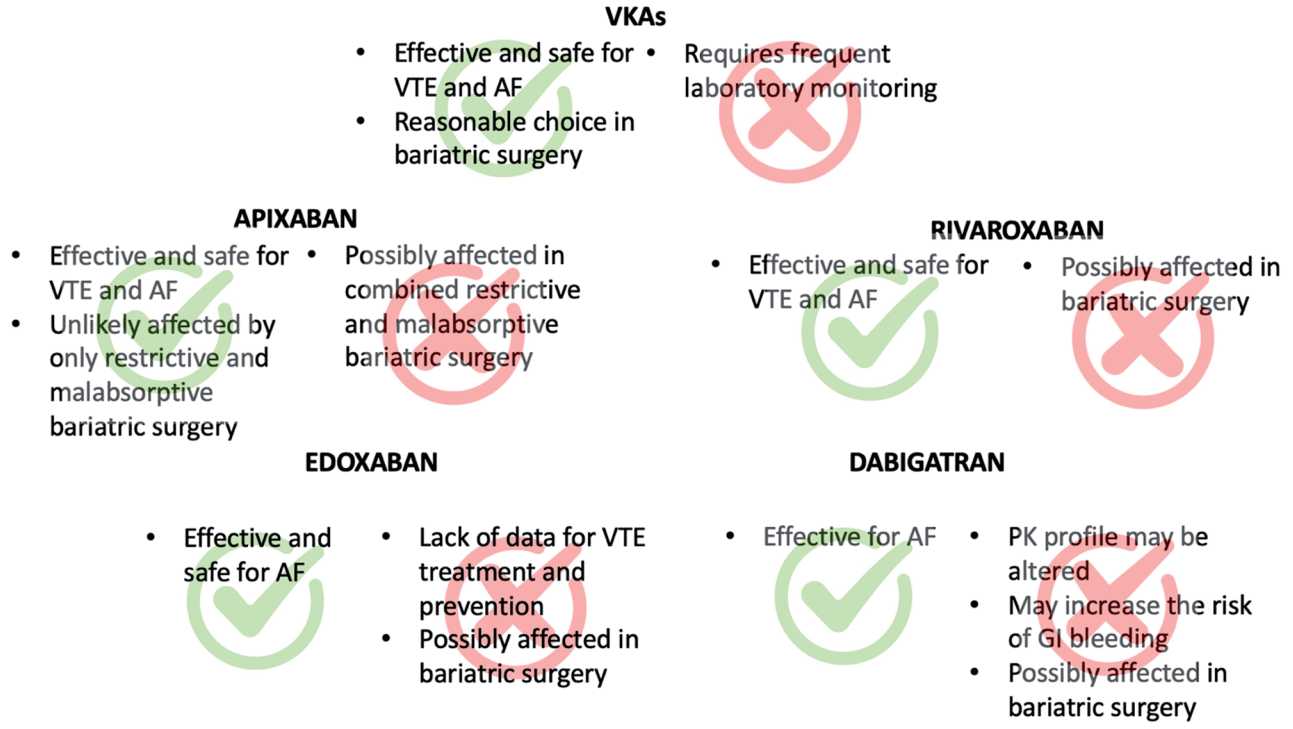

Figure 1. Advantages and disadvantages of oral anticoagulants in morbidly obese patients.

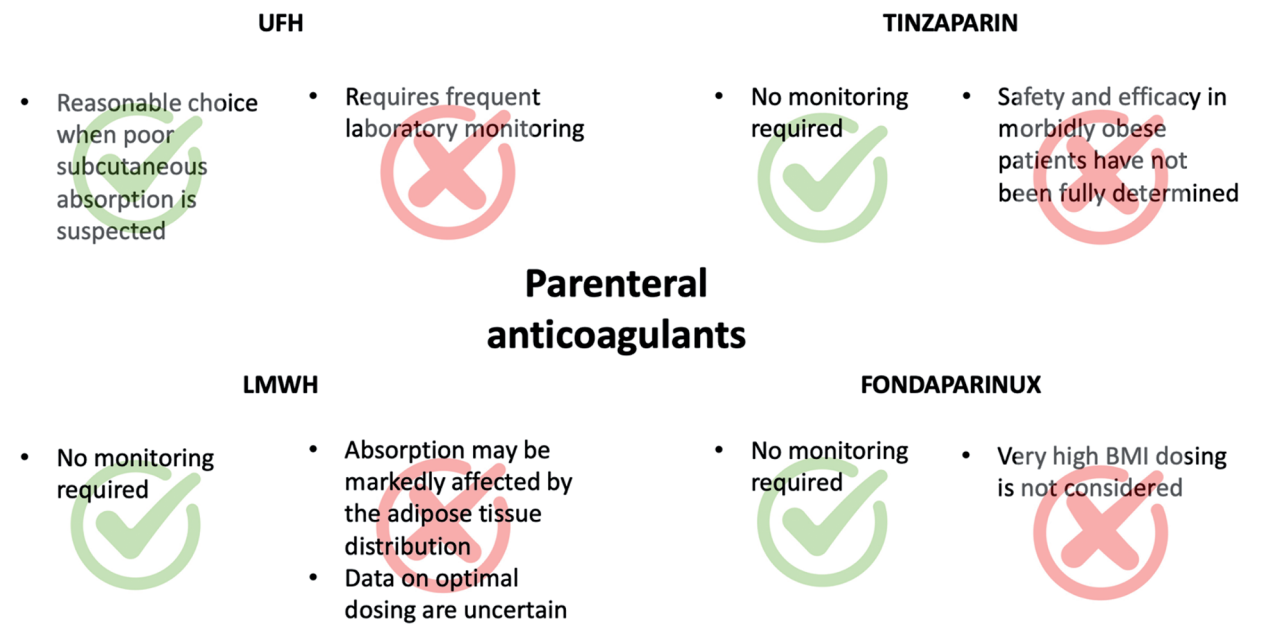

Figure 2. Advantages and disadvantages of parenteral anticoagulants in morbidly obese patients.

In patients with BMI >30 kg/m^2 our suggestion is to prefer the LMWH twice daily administration for both prophylaxis and therapeutic dosing, as it may provide a constant steady state exposure. When available, the anti-Xa factor levels should be measured 2 to 4 h after drug administration, in order to allow an optimal dosage adjustment.

In our practice, we tend to avoid tinzaparin and fondaparinux in patients with very high BMI, as safety and efficacy of these drugs in morbidly obese individuals have not been fully determined yet (Figure 2).

Conclusions

In conclusion, management of anticoagulation in obese patients is challenging and requires a patient-tailored approach. The current protocols using oral and parenteral anticoagulants have scarcely been investigated in the population of obese patients. The pharmacokinetics and pharmacodynamics of anticoagulants administered both orally and subcutaneously can be significantly affected in this population, as a consequence of altered absorption and altered distribution in fat tissue. Hence, these patients may have an increased risk of both thromboembolic events and bleeding complications. It is, therefore, essential for clinicians to recognize these complexities and to use appropriate dosing and personalized strategies, based on current knowledge from the literature associated with laboratory measurement of anticoagulant activity of oral and parenteral drugs to guarantee safety and efficacy of the anticoagulant treatments in obese patients.

Future research is needed to guide and improve our clinical practice, with *ad hoc* designed studies, investigating anticoagulation in obese patients.

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