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***Thromboembolic events in bariatric surgery***

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## THROMBOEMBOLIC EVENTS IN BARIATRIC SURGERY

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## Abstract

**Background:** The escalating prevalence of obesity demands an effective but also safe approach of the patients. The physician has the challenging task of selecting the most adequate approach for each patient. Bariatric surgery is the treatment with the highest success rate in severe cases of obesity. However, like every surgical procedure, is not risk free and complications often occur, such as venous thromboembolism. Thromboembolic events, such as deep vein thrombosis and pulmonary embolism, contribute to the increase of morbimortality rate. In furtherance of preventing this deadly complication it is imperative to establish an optimal prophylactic plan. Nonetheless, this preventive approach remains debatable. The aim of this review is to analyse the previous literature to identify the risk factors for venous thromboembolic events, determine the clinical approach according to the risk and establish the ideal prophylaxis protocol after bariatric surgery. **Methods:** A literature search was performed in PubMed, with “bariatric surgery”, “thromboembolism” and “thrombosis” as searching terms. Then, exclusion and inclusion criteria were applied for final selection of studies. **Results:** The most significant risk factors for venous thromboembolism are high body mass index, previous history of venous thromboembolism, presence of congestive heart failure, laparoscopic Roux-en-Y gastric bypass operation, a long operative time and receiving a transfusion. Using a risk calculator, it is possible to sum up all the risks for each individual and attribute a score. With the thromboembolic risk score and the haemorrhagic risk, it is possible to determine the most appropriate prophylactic plan for each patient. Risk calculators specific for bariatric surgery are not yet validated. Regarding prophylactic approaches, preoperative assessment with duplex ultrasound should only be performed in high-risk patients. Early ambulation and the use of mechanical prophylaxis (use of compression stockings and/or intermittent pneumatic compression) are recommended in all patients. Pharmacological prophylaxis is recommended for all patients in whom the bleeding risk does not exceed the risk of thromboembolism. The dose of pharmacological prophylaxis, its initiation and duration are topics of controversy. The use of inferior vena cava filters should be evaluated on a case-by-case basis, in patients with high thromboembolic risk. In the long term, there is a decrease in the risk of thromboembolism that compensates for the surgical intervention and the short-term risk. **Conclusion:** The patient's approach should be based on the set of individual risk factors. The recommended prophylaxis for all patients includes early ambulation and mechanical prophylaxis. Depending on the patient's risk, pharmacological prophylaxis, the use of inferior vena cava filters and preoperative assessment with duplex ultrasound may be considered.

**Keywords:** bariatric surgery; thromboembolism; thrombosis.

## Resumo

**Contextualização:** A crescente prevalência da obesidade exige uma abordagem eficaz, mas simultaneamente segura dos doentes. O médico tem a incumbência desafiante de eleger a abordagem mais adequada para cada doente. A cirurgia bariátrica é o tratamento com a maior taxa de sucesso em casos graves de obesidade. No entanto, como qualquer intervenção cirúrgica, não é isenta de riscos e, frequentemente, ocorrem complicações, tais como o tromboembolismo venoso. Os eventos tromboembólicos, tais como a trombose venosa profunda e a embolia pulmonar, contribuem para o aumento da taxa de morbimortalidade. Com o intuito de prevenir esta complicação mortal, é imperativo traçar um plano profilático otimizado. No entanto, esta abordagem de prevenção continua a ser controversa. O objetivo desta revisão consiste em analisar a literatura existente de forma a identificar os fatores de risco para eventos tromboembólicos venosos, determinar a abordagem clínica de acordo com o risco e estabelecer o protocolo de profilaxia ideal após cirurgia bariátrica. **Métodos:** Procedeu-se a uma pesquisa bibliográfica na PubMed, com "cirurgia bariátrica", "tromboembolismo" e "trombose" como termos de pesquisa. Subsequentemente, os estudos foram selecionados de acordo com critérios de exclusão e inclusão para serem revistos. **Resultados:** Os fatores de risco tromboembólicos mais relevantes são o elevado índice de massa corporal, a história prévia de tromboembolismo venoso, a presença de insuficiência cardíaca congestiva, a cirurgia laparoscópica de *bypass* gástrico em Y de Roux, o tempo cirúrgico prolongado e a necessidade de transfusão. Utilizando uma calculadora de risco é possível fazer a soma de todos os riscos de cada indivíduo e atribuir um *score*. Com o *score* de risco tromboembólico e com o risco hemorrágico é possível determinar o plano profilático mais adequado para cada doente. As calculadoras de risco específicas para cirurgia bariátrica ainda não estão validadas. Relativamente a abordagens profiláticas, a avaliação pré-operatória com ecografia doppler apenas deve ser realizada em doentes de alto risco. A deambulação precoce e a utilização de profilaxia mecânica (uso de meias elásticas e/ou compressão pneumática intermitente) estão recomendadas em todos os doentes. A profilaxia farmacológica está recomendada para todos os doentes em que o risco hemorrágico não ultrapasse o risco de tromboembolismo. A dose dos fármacos, o início e a duração da profilaxia são temas controversos. O uso de filtros da veia cava inferior deve ser avaliado caso a caso, em doentes de alto risco tromboembólico. A longo prazo, verifica-se uma diminuição do risco de tromboembolismo que compensa a intervenção cirúrgica e o risco a curto prazo. **Conclusão:** A abordagem do doente deve ter por base o conjunto de fatores de risco individuais. A profilaxia recomendada para todos os doentes passa por deambulação precoce e profilaxia mecânica. Conforme o risco do doente pondera-se a profilaxia farmacológica, o uso de filtros da veia cava inferior e a avaliação pré-operatória com ecografia doppler.

**Palavras-chave:** cirurgia bariátrica; tromboembolismo; trombose.

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**List of abbreviations**

AACE - American Association of Clinic Endocrinologists

ASMBS - American Society for Metabolic and Bariatric Surgery

ASA - American Society of Anaesthesiologists

BMI - Body Mass Index

CT - Computed Tomography

DVT - Deep Vein Thrombosis

GCS - Graduated Compression Stockings

IPC - Intermittent Pneumatic Compression

IVCF - Inferior Vena Cava Filters

LMWH - Low-Molecular-Weight Heparin

LRYGB - Laparoscopic Roux-en-Y Gastric Bypass

LSG - Laparoscopic Sleeve Gastrectomy

MBSC - Michigan Bariatric Surgery Collaborative

OMA - Obesity Medicine Association

PE - Pulmonary Embolism

PSMVT - Portal-Splenic-Mesenteric Vein Thrombosis

TEP - Thromboembolic Prophylaxis

TOS - The Obesity Society

UEDVT - Upper Extremity Deep Vein Thrombosis

UFH - Unfractionated Heparin

VTE - Venous Thromboembolic Events

## 1. Introduction

Obesity is an established global disease directly associated with increased mortality and morbidity. The rising prevalence is a reality that overloads the health system due to the extensive list of correlated morbidities: cardiovascular diseases, venous insufficiency, sleep apnoea syndrome, obesity hypoventilation syndrome, type 2 diabetes, chronic kidney disease, urinary stress incontinence, non-alcoholic fatty liver disease, degenerative joint diseases, gastro-oesophageal reflux, abdominal wall hernia, metabolic syndrome, and cancer.(1-3)

The physician's role is to identify patients at risk and select which approach is more adequate for each case.(1) Bariatric surgery, which includes gastric sleeve and bypass, is considered the gold standard in cases of severe obesity. It has shown remarkable results in weight loss, far better than diet, lifestyle changes, and medication combined. (2, 4-8) The criteria for a patient to be a candidate for bariatric surgery are body mass index (BMI)  $>40 \text{ Kg/m}^2$  or BMI  $>35 \text{ Kg/m}^2$  and one or more severe associated weight-related complications correctable by weight loss.(1, 3) Beyond weight loss, studies(1) have shown a reduction of obesity-related co-morbidities, improved glycaemic control in patients with type 2 diabetes and improved cardiovascular outcomes after bariatric surgery. Nevertheless, this surgical procedure is responsible for a higher risk of venous thromboembolism, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE).(2, 4, 5) Venous thromboembolic events (VTE) are associated with considerable postoperative morbimortality and are one of the major causes of early readmission after bariatric surgery.(9) Al-Mazrou et al.(10) reported a spike of hospital readmissions caused by thromboembolic events during the second postoperative week. The incidence of VTE after bariatric surgery varies between 0.06% to 5%, despite the use of thromboembolic prophylaxis (TEP).This is a modest percentage, yet the growing prevalence of obesity and bariatric surgery may give rise to a reasonable rate of VTE events.(4-6, 9, 11-18) Furthermore, the reported incidences appear to be underestimated due to several factors including asymptomatic VTE, lack of data from the private sector or even administrative limitations of the databases.(9)

There are multiple strategies that can be used to prevent VTE after bariatric surgery, such as early ambulation, pharmacologic and mechanical prophylaxis, and use of inferior vena cava filters (IVCF).(1, 2, 5, 9, 19, 20) Different regimens can be used depending on the onset time (preoperative, intraoperative, or postoperative), the duration (24 hours, during the hospital stay, 2 weeks or 1 month postoperatively), the type of mechanical prophylaxis, the type of drug used and the dosage.(1, 2, 5, 9, 12, 17, 20) However, the optimal prophylaxis protocol after bariatric surgery is still uncertain and debatable.(2, 5, 9, 12, 21-23) The goal of this review is to scrutinize the previous literature to identify the risk factors for VTE, determine the clinical approach for each patient according to his risk and establish the optimal prophylaxis regimen, so that the venous thromboembolic events can be predicted and prevented in time.



## 2. Methods

### Search Strategy

A literature search was performed in PubMed for published articles of all types of thromboembolic events after any type of bariatric surgery. The searching terms used were “bariatric surgery”; “thromboembolism”; “thrombosis”.

Search equation: *bariatric surgery* AND *thromboembolism* AND *thrombosis*.

The search was limited to articles published in the last ten years (2011 - April 1, 2021), which led to a total of eighty-nine results.

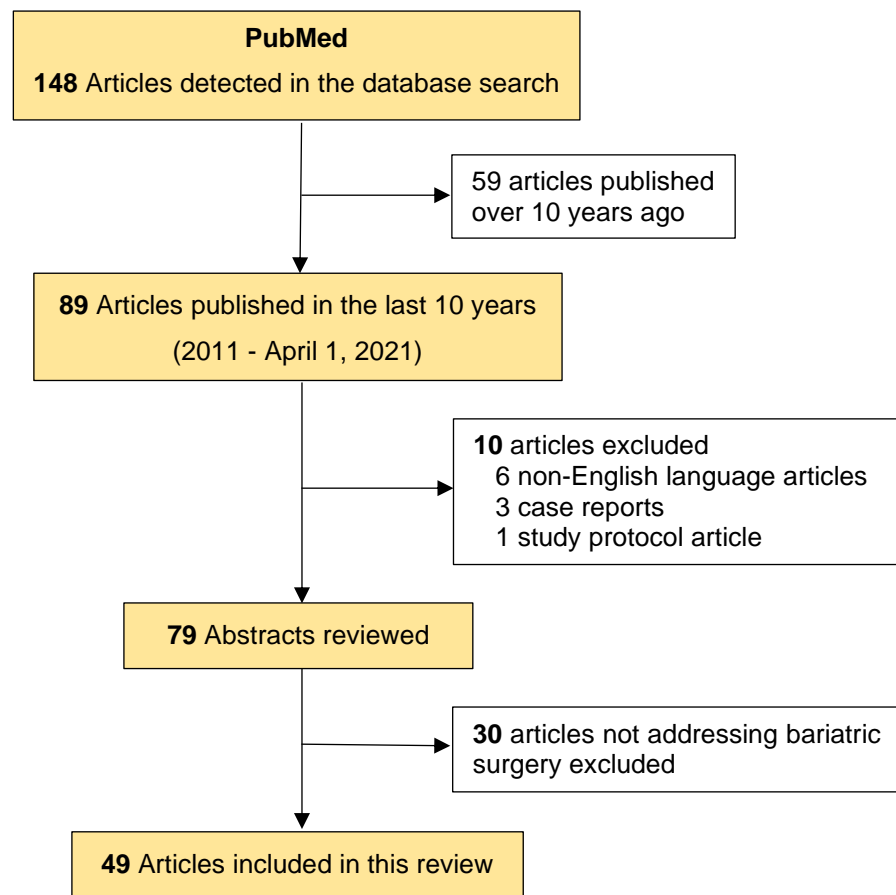
### Study selection

*Inclusion criteria:* English language only; Patients undergoing bariatric surgery only.

*Exclusion criteria:* Case reports; Study protocol articles.

Following the primary literature search, all articles were screened to guarantee that the inclusion and exclusion criteria were fulfilled. After the selection, forty-nine papers remained that were further reviewed.

**Figure 1** Flow Diagram of Studies Included in the Review



### 3. Results

#### 3.1. Epidemiology and risk factors for VTE

The incidence of VTE after bariatric surgery fluctuates between 0.06% to 5%, which is a modest rate, but the rising prevalence of obesity and bariatric surgeries can originate a reasonable number of VTE events.(4-6, 9, 11-17). To prevent these events is essential to understand which factors can increase the risk, with the aim of being able to minimize them. The risk factors for VTE can be divided in two groups, the patient-related and the procedure-related.

From the **patient-related** risk factors, stand out the male sex, black race,(13) increasing age, higher BMI, previous history of VTE(24), thrombophilias(1) and oestrogen therapy(25). Patient smoking status(11), alcohol abuse, and presence of congestive heart failure were also associated with potential risk.(4, 5, 13, 16, 17, 21, 26)

Obesity ( $BMI \geq 30 \text{ kg/m}^2$ ) is a major risk factor for VTE(18) and it was demonstrated that the risk of VTE increases 37% for every 10-unit increment in BMI.(5) Adipose tissue is an important source of inflammatory mediators that directly interfere with the regulation of the coagulation cascade (increased levels of coagulation factors VII and VIII, von Willebrand factor, thrombin, fibrinogen and plasminogen activator inhibitor 1).(27) This implies that patients with obesity are permanently in a state of hypercoagulability, which in fact increases the risk of VTE.(9, 17) Moreover, there is a restriction of mobility with increasing BMI, resulting in venous stasis of the lower limbs, and increasing the risk of VTE.(28)

The existence of a previous VTE event quadruplicates the risk of a postoperative VTE.(5)

Hollander et al.(29) observed that a higher BMI is associated with an increased risk of thrombophilia. Such may be explained by diminished hepatic synthesis of coagulation factors caused by hepatic steatosis. Meanwhile, inherited or acquired disorders of the coagulation system contribute to the cumulative risk for VTE.(1, 29)

In laparoscopic bariatric surgery, the diagnosis of congestive heart failure increases 4.64 times the risk of DVT and 6.03 times the risk of PE.(16) The reason for this increased risk is not exactly known. It is established that these patients have a reduced ejection fraction, which leads to venous stasis in the lower extremities. Additionally, patients with chronic heart failure present endothelium dysfunction and a hypercoagulable state, justified by increased plasma viscosity and elevated level of von Willebrand factor. Consequently, these patients reunite all the factors of Virchow's triad (stasis of blood flow, endothelium injury and hypercoagulability), which can justify the increased risk of VTE.(16)

The **procedure-related** risk factors comprise the length of the operation, if is open or laparoscopic, the type of the procedure, and the postoperative complications.(5, 17)

M. M. Chan et al.(30) observed that the duration of the operation (longer than 180 minutes) was the only independent factor influencing the risk of VTE in their study. So, the longer the duration of surgery, the more significant is the risk of postoperative VTE.

Although some studies(4, 17, 30) indicate that laparoscopic surgery has a shorter operative time and therefore is less associated with VTE risk and present lower mortality rates from PE than open surgery(1), there is no firm evidence supporting the superiority of laparoscopy.(8, 9, 24, 31, 32) In fact, during laparoscopic surgery involving the reverse Trendelenburg position, due to excess weight and pneumoperitoneum at 15 mmHg,(31) there is an increase in abdominal pressure which builds up pressure on the inferior vena cava, iliac veins, and femoral veins, lowering 50-60% the venous flow,(15) and causing venous stasis in the lower limbs.(3, 9, 17, 21, 29) Additionally, the induction of pneumoperitoneum causes oxidative stress that leads to endothelium dysfunction.(17) In this way there is a basal state of hypercoagulability due to obesity, with venous stasis and endothelial dysfunction, which can easily culminate in thrombotic events. One can easily understand that the longer the surgery, the greater the exposure to these procoagulant factors and higher the risk of VTE.(3, 4, 17, 29, 30).

Comparing different types of surgeries, adjustable gastric band procedures are considered the ones with less risk of VTE comparing with laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB). However, the gastric band procedures are no longer a first-line weight-lost surgery.(4, 5) Between, the two standard procedures, Gambhir et al.(4) demonstrated that LSG has less 30% risk of VTE than LRYGB. This difference is not explained by the length of the operative time, but by the complexity of the LRYGB operation(24), which involves the creation of two anastomoses and entails a higher risk of endothelial injury. The LRYGB operation is also associated with more postoperative complications, such as anastomotic leakage,(1, 11, 13) which prolong the immobilisation time, and consequently increase the risk of VTE.(4, 9)

Regarding postoperative complications, Celik et al.(24) observed that the risk of VTE in patients with postoperative complications was 3.6% versus 0,6% in patients without complications. This can be explained by the increased inflammatory response, the increased immobilisation time and the greater risk of dehydration that enhances the hypercoagulable state.(24)

Gambhir et al.(4) demonstrated that receiving a transfusion increases 4 times the odds of DVT and 5 times the risk of PE. This superior risk can be justified by the pro-inflammatory effects of the donated red blood cells which lead to a state of hypercoagulability. Also, the TEP is withheld when patients bleed to the point of needing a transfusion, which furthermore increases the risk.(1, 4, 5, 9, 33)

Gambhir et al.(4) observed that the most significant risk factors for VTE after LSG and LRYGB are the existence of previous VTE, receiving a transfusion and a long operative time.

### 3.2. VTE physiopathology

First described by Virchow in 1856, the pathophysiology of thromboembolic events is still valid today. According to the theory, clot formation can be explained by the association of three factors, the so-called Virchow triad (hypercoagulability, venous stasis, and endothelial lesion of the vessel wall).(13) The patients who undergo bariatric surgery usually have already a hypercoagulable basal state,(15) either due to genetic or acquired factors, which justifies the increased risk of a VTE reoccurring when there is a previous history of VTE. Obesity itself leads to a state of hypercoagulability via a chronic inflammatory process and fibrinolysis dysfunction, with increased plasma concentration of coagulation factors and plasminogen activator inhibitor-1.(34) Additionally, venous stasis may also be an issue in these patients, either due to a prolonged surgical time and a decreased mobility. Finally, with surgery there may also be endothelial damage to the vessel wall that activates von Willebrand factor and leads to platelet aggregation.(13)

Normally, the elements of Virchow's triad are brought together in the deep venous circulation of the lower limbs, resulting in the formation of a thrombus and consequent deep vein thrombosis. However, this thrombus can migrate to the pulmonary circulation and give rise to a pulmonary embolism. In more unusual cases, the thrombus may even form in the upper limbs as well as in the portal venous circulation.(13)

### 3.3. Types of thromboembolic events

**Pulmonary embolism** is described as the lodging of blood clot in a pulmonary artery diagnosed by ventilation-perfusion scan, computed tomography (CT) scan or pulmonary arteriogram within 30 days of the operation.(16) PE is responsible for 40 % of all deaths within the first 30 days of postoperative and is a frequent discovery at autopsies.(1, 5, 8, 11, 33) The symptoms presented can be very variable from an asymptomatic presentation of mild tachycardia to a severe case of hypoxaemia.(8) Postoperatively, the presentation of respiratory distress or failure in weaning from ventilatory support shall immediately raise awareness on the diagnosis of PE.(1)

**Deep vein thrombosis** is defined by the formation of a fibrin clot in the venous circulation of the lower limbs,(13) diagnosed by duplex ultrasound, contrast venography, CT scan or magnetic resonance venography within 30 days of the operation.(16) Note that duplex ultrasound has low sensitivity in patients with obesity,(8) as they have larger lower limbs and the panniculus adiposus around the inguinal region may completely cover the visibility of the pelvic veins.(35)

**Upper extremity deep vein thrombosis** (UEDVT) is defined by the formation of a fibrin clot in the venous circulation of the upper limb and represents less than 10% of DVT events.(28) Safdie et al.(28) observed that 80% of patients with UEDVT complained about local pain and 40% presented inflammatory signs such as oedema and erythema. The first-line test for

UEDVT diagnosis is the duplex ultrasound, that by the shadow effect caused by the sternum and clavicle, has lower sensitivity and specificity in the upper limb vs. the lower limb. When necessary, recourse can be made to contrast venography. UEDVT can complicate with symptomatic PE in 3 to 12% of cases, so anticoagulation should be started as soon as possible. The standard anticoagulation regimen relies on intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH), which is followed by a minimum of 3 months of oral warfarin.(28)

**Portal-splenic-mesenteric vein thrombosis (PSMVT)** is defined by the formation of a fibrin clot in the venous portal circulation and is a rare but life-threatening complication that can result in intestinal ischemia and infarction.(1, 6, 22, 36) PSMVT is more frequent in patients undergoing LSG,(25, 36) which can be explained by the closer contact with the splanchnic and superior mesenteric veins involving greater risk of endothelial injury and by the diminished venous flow due to the ligation of the short gastric vessels and dehydration.(22) When risk factors for PSMVT (contraceptive therapy, congenital thrombophilia, smoking and LSG procedure) are present, Caruso et al.(36) recommend prophylaxis with enoxaparin 40 mg subcutaneously twice daily for 4 weeks. About 50% of patients are asymptomatic but when symptoms do occur, in general they are nonspecific. Abdominal pain is the only symptom shared by all patients. The gold standard test for PSMVT diagnosis is the abdominal and pelvis CT enhanced with oral and intravenous contrast.(6, 22) When there is no intestinal ischaemia, treatment should be started immediately with anticoagulation using the same prescription as in the UEDVT. In cases where peritonitis or shock is already apparent, an exploratory laparotomy with possible resection of the necrotic bowel is necessary.(22, 36)

#### 3.4. VTE risk assessment

Each patient has a smaller or larger set of risk factors, which are summed up and together contribute to the individual risk of VTE. To determine this overall risk, it is possible to use risk calculators, which, based on each patient's clinical information, calculate the individual risk of VTE. Based on this individual risk, it is possible to decide which prophylaxis should be used, giving the right prophylaxis to high-risk patients and avoid unnecessary approaches in low-risk patients.(20) For this reason, the use of VTE risk calculators is recommended, according to the 2019 guidelines of the American Association of Clinic Endocrinologists, The Obesity Society, the American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anaesthesiologists (AAACE/TOS/ASMBS/OMA/ASA).(1) There are several risk assessments models that have been used for a long time to assess the risk of VTE in other types of surgery. The most widely used is undoubtedly the Caprini score,(13) which through the assessment of 37 to 40 patient-related and procedure-related risk factors rates patients with a total risk factor score.(20) According to The American College of Chest Physicians, patients can be divided into very-low-risk (Caprini score 0), low-risk

(Caprini score 1-2), moderate-risk (Caprini score 3-4) and high-risk (Caprini score 5 or more). The Caprini score was developed in 2005 and is not validated yet in bariatric surgery(13), however, experts currently accept its use.(20)

There are other models of risk calculators specific to bariatric surgery but are not validated also, such as Michigan Bariatric Surgery Collaborative's risk calculator (MBSC) and BariClot.(4) The MBSC risk calculator was developed in 2012, to help predict the risk of VTE after bariatric surgery, however it may only have a regional application since it was created from a relatively small and limited database.(13) On the other hand, Dang et al.(13) developed BariClot in 2018, supported by an extensive database, containing information regarding 95% of the bariatric surgeries performed in the United States. However, the major limitation of this tool was the lack of data on VTE prophylaxis, with Dang et al.(13) assuming in their study that most patients without contraindications took prophylaxis. It should be noted that all these models don't incorporate transfusion as a risk factor.(4) Nevertheless, Gambhir et al.(4) demonstrated that receiving a transfusion significantly increases the risk of VTE, so to achieve more accurate risk calculations, the inclusion of this variable should be considered.

But that's not all, there is another factor, besides the risk of VTE, that should be considered when it comes to the decision of prophylaxis. So, to prevent VTE after bariatric surgery, different approaches can be applied, such as early ambulation, mechanical and pharmacological prophylaxis.(1) However, these interventions are associated with a higher risk of bleeding, especially pharmacological prophylaxis.(20) Therefore, to obtain a more tailored prophylaxis, it is important to assess the risk of thrombosis, but also the risk of bleeding.(5, 20) Unlike the risk of VTE which has been targeted for assessment in several studies, the risk of haemorrhage has been poorly assessed since patients at high bleeding risk are often excluded from studies. Therefore, assessments of haemorrhagic risk are made based on expert opinions, and none are validated.(20) Empirically, based on the presence of risk factors (among them, previous major bleeding, untreated bleeding disorder, thrombocytopenia, uncontrolled hypertension or complex surgery), patients are classified as high-risk or not, without having a score or a defined cut off.(20)

### 3.5. VTE prophylaxis and prevention

Many different approaches can be applied to prevent VTE after bariatric surgery, such as early ambulation, mechanical and pharmacological prophylaxis. However, there is no optimal plan that indicates which mechanisms should be used, when or how.(2, 5, 9, 12, 21-23) This absence of a precise guideline has resulted in meaningful disparities being created between surgical centres regarding VTE prophylaxis, especially about treatment length and the dose of pharmacological prophylaxis.(18)

### **3.5.1. Pre-operative screening venous duplex ultrasound**

Multiple studies have associated obesity by itself with a high-risk of developing idiopathic DVT.(37) Well, patients with obesity tend to present high intra-abdominal pressure, reduced venous flow in the femoral veins, limited mobility, and osteoarthritis, which result in venous stasis of the lower limbs and facilitate thrombus formation. As a result, in some surgical centres, all patients are routinely screened pre-operatively for DVT, due to potential legal issues.(37) However, Raj et al.(37) showed that preoperative DVT is a very rare condition, so this assessment with venous duplex ultrasound should only be performed preoperatively in high-risk patients.(24, 27) Patients with BMI >50 kg/m<sup>2</sup>, elderly, previous history of DVT, history of heart failure, previous surgery and superficial venous disease should be considered high risk.(37) According to AACE/TOS/ASMBS/OMA/ASA guidelines(1), patients with a history of DVT or cor pulmonale need to be assessed for risk to bariatric surgery and undergo proper diagnostic screening for DVT.

### **3.5.2. Setting the patient up on the operating table**

At the very beginning of the surgery and with a basic and simple gesture, measures to prevent VTE can begin to be taken. During the positioning of the patient on the operating table, particular care must be taken to ensure that it is adequate and comfortable, to avoid limb compression and consequent vascular damage. (28)

### **3.5.3. Mechanical thromboembolic prophylaxis**

The mechanical methods of prophylaxis have as their modus operandi the lower extremities compression, with the goal of decreasing venous stasis of the lower limbs. There are two main methods, the use of compression stockings and intermittent pneumatic compression (IPC).(5) Most authors advocate the use of one of these methods, but for instance the Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery recommend the use of both methods in all patients.(5)

IPC is accomplished with a device that insufflates and sequentially pressurizes the lower limbs, simulating muscle contractions. The purpose of this technique is to diminish venous stasis of the lower limbs, especially during surgery and in post-operative immobility periods.(5, 21) A meta-analysis of studies has demonstrated a reduction in the risk of VTE of approximately 60% when IPC is adopted.(5, 31) The recommendation is to start IPC when anaesthesia is induced and keep it up to 24 hours postoperatively.(22)

The most frequent alternative to IPC is the use of graduated compression stockings (GCS). These should start being used as soon as patients are admitted to hospital, maintained during the hospital stay and then up to 7 days after discharge.(5, 22) Of note, there are a few complications associated with use of compressive stockings such as blisters, skin breakdowns, ulceration, and necrosis.(5)

### **3.5.4. Early Ambulation**

According to several guidelines(1, 5), it is recommended to start walking early after surgery, usually 4-6 hours later, under assistance, as it has been proven to decrease venous stasis in the lower limbs.(22, 28) Although effective, early ambulation cannot be used as the only method of prophylaxis and should therefore be used as an adjuvant method.(5)

### **3.5.5. Pharmacologic thromboembolic prophylaxis**

#### ***Selection of the pharmaceutical drug***

The only drug used for TEP in bariatric surgery is heparin. Between LMWH and UFH, LMWH are easier to use, have enhanced bioavailability and more predictable pharmacokinetics,(27) longer half-life and present a slightest risk of heparin-induced thrombocytopenia.(5, 17) Multiple clinical studies(5) revealed a 71% reduction of VTE risk when LMWH was administered as prophylaxis compared with placebo or no prophylaxis. However, LMWH administration also increases the haemorrhagic risk by 2.03 times when compared with the control group.(5) Some studies have tried to compare UFH with LMWH in the prevention of VTE in bariatric surgery, but they presented certain limitations and failed to obtain clear results, both in terms of prophylactic efficiency and haemorrhagic risk.(5) Bearing in mind that there is no documented superiority of a single option, the use of either UFH or LMWH is reasonable, according to ASMBS.(1, 5, 35) Alternatively, fondaparinux 5mg once a day can be used as a preventive pharmaceutical choice.(1, 17) Steele et al.(35) conducted a double-blinded study comparing fondaparinux with enoxaparin and found that anti-factor Xa levels were indeed more appropriate with fondaparinux, but overall, the rate of DVT was similar between the two groups.(27)

Additionally, it is worth citing a particular group of patients who are under chronic vitamin K antagonist therapy having an extra factor disturbing the balance between bleeding and thrombosis in the perioperative period. Usually, the procedure is bridging with LMWH or UFH and closely monitoring the international normalized ratio during perioperative time.(38)

The use of LMWH as prophylaxis has also drawbacks such as the subcutaneous administration, the need of monitor hematologic parameters, the drug interactions and risk of osteopenia.(17) Alternatively, the direct oral anticoagulants could be a practical and effective solution. Some studies(17) demonstrated that rivaroxaban and apixaban, two factor Xa inhibitors, have better efficacy than LMWH. But these anticoagulants are absorbed in small intestine and there is no solid data that proves the same efficacy after bariatric surgery, especially in malabsorptive procedures.(17, 20) Malabsorptive surgery leads to changes in gastrointestinal anatomy, affecting gastric emptying time, interfering with pH, decreasing small intestinal transit and disturbing gut microbiota.(2) All this can interfere with the absorption of oral anticoagulants.(2) Besides, bariatric surgery results in an accentuated weight loss with a decrease of adipose tissue, which can affect the distribution and metabolization of the oral



anticoagulants.(2) Kröll et al.(2) followed a group of 12 patients taking rivaroxaban after bariatric surgery and concluded that there was no change in the pharmacokinetic or pharmacodynamic parameters of rivaroxaban over 6 to 8 months. However, for now, these drugs are not part of the recommended pharmacological weapons employed in VTE prophylaxis.(5, 20) However, soon and with larger studies to prove their efficacy and safety in the context of post-bariatric surgery, these medicines may well become a good option.

### **Pharmaceutical Dose**

The ideal dose of heparin in patients with obesity undergoing bariatric surgery is a matter of controversy, but it is imperative to establish an optimal dose so that a balance can be maintained between the risk of VTE and the risk of haemorrhage.(5, 11, 17, 27) Moulin et al.(18) collected data from thirty-seven surgical centres in France and found that doses of pharmacological prophylaxis ranged substantially between values of 4000 to 12000 IU per day. The dose traditionally used in patients without obesity as prophylaxis of VTE is 30 mg (subcutaneous twice a day) or 40 mg (subcutaneous once a day) of LMWH or 5000 IU (subcutaneously 2-3 times a day) of UFH.(17, 25) Nevertheless, in patients with obesity the literature is not precise, but normally the standard regime used in TEP is LMWH (30 mg twice a day or 40 mg twice a day) or UFH (5000 to 7500 IU subcutaneously 2-3 times a day).(5, 17, 25, 27)

The LMWH bind to antithrombin, changing its structure, resulting in the inactivation of thrombin and factor Xa, and consequently serving as an anticoagulant.(25) Therefore, the suitability of the heparin dose in preventing VTE can be monitored by the measurement of anti-factor Xa levels.(1, 25) This measurement can be performed in the operation day and on postoperative day 3 and 7.(17) However, the regularity of assessment varies significantly between surveys.(25) Anti-factor Xa levels between 0.2 and 0.5 IU/ml, when measured 3 to 5 hours after administration, are thought to be an indicator of an adequate drug dosage for prophylaxis.(25, 27, 39) Anti-factor Xa values above 0.5 must be considered therapeutic anticoagulation.(25) The measurement of anti-factor Xa levels is practical and inexpensive,(25) but requires precise time measurements, which is not always easy in medical practice(27) and gives no precise information about bleeding risk, which significantly limits his use.(5, 17) Therefore, it would be advisable to reserve routine anti-factor Xa testing only for high-risk patients with BMI >50 kg/m<sup>2</sup> and those discharged on extended pharmacological prophylaxis.(25)

One study compared two groups of patients receiving different enoxaparin protocols, 30 mg twice a day and 40 mg twice a day, to understand which dosage would provide a better balance between efficacy and safety.(5, 11) It was found that the group of patients who received higher doses of LMWH presented a lower incidence of VTE with no significant difference in the incidence of bleeding.(5, 11) The increased efficacy of the higher dose in patients undergoing

bariatric surgery can be theoretically explained on the basis that obesity interferes with the pharmacokinetics of the drug.(17) Obesity leads to changes in drug absorption, volume of distribution, hepatic metabolization and renal clearance.(40) Accordingly, it is legitimate to question whether standard fixed doses are not sub-therapeutic and whether the dose should not be adjusted to the BMI.(27, 40) According to the United Kingdom Clinical Pharmacy Association, LMWH doses should be weight-based, with 40 mg once daily if weight <100 kg, 40 mg twice daily if weight between 100-150 kg and 60 mg twice daily if weight >150 kg.(27) Therefore, studies(17) were conducted to understand if weight-adjusted doses of enoxaparin (0.5 mg/kg subcutaneously every 12 h) were more effective. There is no consensus on outcomes across studies,(12, 40, 41) but the weight-adjusted doses of enoxaparin seem to be safer and more effective in patients with a BMI > 50 kg/m<sup>2</sup>.(5, 20) Likewise, the presence of VTE risk factors may also be taken into account when adjusting the dose of LMWH, such as age >50 years, male gender, venous insufficiency, obstructive hypoventilation syndrome, smoking and previous history of VTE.(17, 21) On the other hand, the administration of weight-adjusted doses of enoxaparin in patients not displaying VTE risk factors, seems to be associated with an increased risk of bleeding.(9, 17, 21, 42) One study reported that the rate of bleeding with standard doses was approximately 1% and with weight-adjusted doses it was 1.6%.(18)

LMWH is a hydrophilic drug and therefore tends to remain in the extracellular fluid, unlike lipophilic drugs that are easily distributed in adipose tissue.(25) Knowing that intravascular volume does not increase proportionally with weight(42) and that LMWH does not distribute well in adipose tissue, it is easy to understand that with the weight-proportional dose, it is likely that overdose occur, increasing the risk of haemorrhage.(18, 25, 40) Linden A. Karas et al.(25) relied on anti-factor Xa measurement to assess the appropriateness of BMI-based prophylaxis. As such, they administered enoxaparin 40 mg twice a day to patients with BMI <50 kg/m<sup>2</sup> and enoxaparin 60 mg twice a day to patients with BMI ≥50 kg/m<sup>2</sup>. It turned out that following this scheme, overdose occurs much more frequently than underdose. Indeed, in the group with BMI ≥50 kg/m<sup>2</sup> no underdose was reported. This leads us to the belief that the standard dose may be insufficient, and the weight-adjusted dose can be excessive, so an intermediate value would be ideal. Imberti et al.(42) compared two groups of patients, one doing prophylaxis with the standard dose of LMWH and another group with a dose 25% higher than the standard, to find the intermediate dose. However, both groups achieved the same efficacy with similar bleeding rates.

Given the hydrophilic characteristics of LMWH and knowing that they are better distributed throughout lean mass than fat mass, if the LMWH doses were adjusted to lean mass, theoretically better results could be obtained.(39) Bearing this in mind, Schijns et al.(39) have effectively proven that anti-factor Xa activity varies inversely proportionally with lean mass and more strongly than with body weight. Based on this premise they developed an algorithm to

generate the dose of LMWH according to the patient's lean mass and the target anti-factor Xa level. It is not known whether the application of this formula in practice reduces the risk of VTE without increasing the risk of haemorrhage, but with more widespread and robust studies, the solution might be found in this direction.(39)

It is understandable that the standard dose of heparin for prophylaxis is not optimal, but current data are unable to state if the ideal method involves a higher dose regardless of BMI, a weight-adjusted dose, a dose adapted to risk factors or perhaps even monitoring the dose by checking the level of anti-factor Xa. There is a strong need for large randomized controlled trials in patients with obesity undergoing bariatric surgery to collect robust and reliable data.(18)

### ***Onset time and duration***

According to the standard procedure, the LMWH must be initiated before the surgery and sustained postoperatively for the length of hospital stay.(17, 20, 21, 28) Yet, this protocol has not proven to be better than any other and there is often no mention in the guidelines of when to start the prophylaxis and for how long it should be maintained.(5) For example, in 2013, the AACE/TOS/ASMBS/OMA/ASA(1) recommended that pharmacological prophylaxis should be instituted within 24 hours of surgery and did not mention the duration of therapy.(5) In 2019, the recommendations changed, and pharmacological prophylaxis must now be started before surgery and maintained during hospitalization if there are no contraindications.(1) As there are no guidelines with exact information on when to start prophylaxis, some surgeons start 1 week before the procedure especially in high-risk patients, others initiate it at the night before or at the very same day of the surgery.(27) Some surgeons also opt to use only pre-operative prophylaxis or only post-operative prophylaxis. When compared, Altieri et al.(23) reported that postoperative prophylaxis presents a lower risk of haemorrhage compared to preoperative prophylaxis.

It is nevertheless important to note that 80% of thromboembolic events take place after the hospital stay,(1, 9, 21) which raises the doubt as to whether the length of prophylaxis should not be extended.(11-13, 43) So, some authors advocate that prophylaxis should be maintained for 2 to 4 weeks,(25, 43) since bariatric surgery is a risky procedure in high-risk patients.(6) Stroh et al.(17) in 2016, demonstrated that patients who receive pharmacologic TEP for more than 2 weeks have 3.62 more risk of DVT in comparison to those who take pharmacologic TEP for less than 1 week. Also, Lindsey N. Clark et al.(43) in 2019, observed that patients receiving pharmacological prophylaxis post-discharge experienced higher rates of VTE post discharge. However, these data might be distorted by a selection bias, since only high-risk VTE patients were enrolled in the extended prophylaxis regimen.(43) Almarshad et al.(11) in 2019, showed effective results in preventing VTE without increasing the bleeding risk, using an extended duration thromboprophylaxis (enoxaparin 40 mg twice daily for 10-14 days). Therefore, the most reasonable approach seems to be reserving the extended prophylaxis for high-risk

patients. In fact, using it for all patients could mean overtreatment for many patients, with an increased risk of haemorrhage for the patients and increased financial burden on the health system.(24)

According to the 2019 AACE/TOS/ASMBS/OMA/ASA guidelines(1), pharmacological prophylaxis after the admittance time should be considered in high-risk patients (with previous history of VTE, known hypercoagulable status, limited ambulation or with a risk of DVT>0.4%, when using risk calculators). The European Society of Anaesthesiology also recommends 10 to 15 days of pharmacological prophylaxis in high-risk patients (aged >55 years; BMI >55 kg/m<sup>2</sup>, history of VTE, venous disease, sleep apnoea, hypercoagulability, and pulmonary hypertension).(11, 20)

### ***Protocol for prophylaxis***

In 2013, the American Society of Metabolic and Bariatric Surgeons considered that patients undergoing bariatric surgery have moderate to high risk of VTE,(23, 35) recommending the use of mechanical prophylaxis and early ambulation, either with or without pharmacological prophylaxis, taking into consideration the clinical judgment and the haemorrhagic risk.(5, 26) This is considered a risk-stratified protocol, in which pharmacological prophylaxis is only given to patients with a family or personal history of hypercoagulable conditions and considering the haemorrhagic risk. However, the universal prophylaxis protocol involves the administration of LMWH to all patients, together with the implementation of mechanical prophylaxis and early ambulation.(5) One study(5) compared both protocols and concluded that the risk of VTE was lower in the group of patients assigned to the risk-stratified protocol. But there is no definition of the actual number of patients who took LMWH in the group assigned to the risk-stratified protocol, limiting the conclusions that may be drawn.(5) Gagner et al.(31) tried to compare the use of mechanical prophylaxis alone with the use of the combination pharmacological and mechanical prophylaxis. However, no results were obtained, mainly because of the small sample size. The study being observational, also presented a significant selection bias, since all the subjects selected to receive only mechanical prophylaxis were patients at low VTE risk. Summing up, although the decision to use pharmacological prophylaxis is based on the physician's clinical judgement, it is wise to only exclude from taking LMWH, patients with a bleeding risk that far exceeds the risk of VTE.(5) Indeed, according to a prospective study published in 2017,(15) the use of LMWH is not only necessary but insufficient. Moaad et al.(15) found that even after prophylaxis with LMWH, patients postoperatively displayed an aggravation of the coagulation profile and an increase in platelet activity. As an alternative, they suggest the concomitant use of anticoagulation and antiplatelet therapy, however such an association is known to seriously increase the haemorrhagic risk.(15)

The American College of Chest Physicians recommends stratification of patients into low, moderate, and high-risk of VTE, using the Caprini score. Generally, candidates to bariatric

surgery are most often at moderate or high-risk of VTE,(5, 20) because this score was created for other types of surgery and overrates the risk in these cases, since 3 points are automatically awarded for high BMI and surgery time of more than 45 min.(13) Regardless of risk stratification, it is not appropriate to restrict thromboembolic prophylaxis to high-risk patients only, since 33% of the patients who experience VTE do not exhibit any additional risk factor besides obesity and the bariatric surgery undertaken.(9) So, using VTE risk stratification but also with haemorrhagic risk, the American College of Chest Physicians recommends a prophylaxis adjusted to each profile (Table 1).(5, 20, 31)

**Table 1** The American College of Chest Physicians' recommendations for VTE prophylaxis(5)

	Not-high bleeding risk	High bleeding risk
Low VTE risk	IPC	IPC
Moderate VTE risk	UFH or LMWH or IPC	IPC
High VTE risk	(UFH or LMWH) and (GCS or IPC)	IPC

Adapted from Bartlett et al.(5) 2015.

**Abbreviations:** VTE, venous thromboembolic events; IPC, intermittent pneumatic compression; UFH, unfractionated heparin; LMWH, low molecular weight heparin; GCS, graduated compression stockings.

### 3.5.6. Inferior vena cava filters

IVCFs are usually placed to prevent venous thrombi from reaching the cardiopulmonary circulation but do not have any effect on the resolution of peripheral or central thrombi.(8) Filters can be permanent or non-permanent and within the non-permanent ones there are two types, temporary filters (filters are attached to an external wire or catheter) and retrievable filters (filters are fitted internally without any external connection, which decreases the rate of infections). The filters approved in these cases are retrievable filters, as they are less risky than permanent filters and maintain protection in short term. (8)

The insertion of IVCF as prophylaxis is a method rarely used in clinical practice,(19) since the studies are very heterogeneous(32, 44, 45) and there is no sufficiently solid evidence to ensure the efficacy of this aggressive and intrusive method or to support IVCF placement as a routine method of prophylaxis after bariatric surgery.(8, 27, 41, 46, 47) Stein et al.(19) reported a decrease in mortality from DVT in patients with a filter, however, the same reduction has not occurred in the number of deaths from PE. Yet, other studies(1, 5, 13, 45, 46) have found opposite outcomes, describing a statistically significant increased risk of VTE in patients who had preoperative IVCF placement. Birkmeyer et al.(48) designed a cohort observational study to evaluate the safety and efficacy of IVCF use and concluded that patients with IVCF have worse outcomes, higher rates of VTE and more complications, essentially associated with IVCF.(8) Also, Li et al.(47) reported that the use of IVCF as prophylaxis is associated with

higher incidence of DVT, higher postoperative mortality and increased hospital fees. Even the guidelines provide different answers, The American College of Chest Physicians strongly opposes to the use of IVCF as primary prevention of VTE, while the American College of Radiology only states there is limited evidence to support the use of IVCF.(46)

One study(5) reported positive results with a decrease in PE mortality in patients with BMI >55 kg/m<sup>2</sup>, who were implanted with an IVCF. Accordingly, IVCF placement seemed to be a more effective method regarding primary prevention of PE in patients at higher risk of VTE.(5) However, there is no evidence that the potential benefit in preventing PE overcomes the risk of complications associated with IVCF.(44) Indeed, considering that PE is the leading cause of preventable perioperative death, IVCFs are often placed in an attempt to reduce the risk of PE.(46) Nevertheless, in 2019, Haskins et al.(14) described no significant differences in the incidence of PE with and without IVCF, as well as no protective effect of IVCF, even in high-risk patients. However, as few patients are assessed for PE compared to the number of patients assessed for DVT, it is important to be aware of a measurement bias. Indeed, the diagnostic rate of postoperative PE is less than 2%, however, in about 80% of autopsies of postoperative patients reveal silent PE.(8, 45)

On the other hand, it may still be the only alternative in cases with a high risk of VTE but also high haemorrhagic risk, which strongly limits the use of the most recommended prophylaxis.(24) Indeed, according to the ASMBS, IVCF placement should be considered as an adjuvant method, in high-risk patients for whom the risk of VTE is significantly higher than the risk of filter-related complications.(5, 8, 32, 36, 44) This would require multiple risk factors for VTE to be present, such as BMI greater than 50, 55 or 60 kg/m<sup>2</sup> (cut offs differ across studies), previous VTE, pulmonary insufficiency and hypertension, history of coagulopathy, immobility, obstructive sleep apnoea or evidence of preoperative lower limb stasis.(8, 32, 44, 45, 47, 49) Furthermore, whenever the placement of an IVCF is thought, the risk of associated complications must be considered.(47) Reddy et al.(46) described an increase in hospital costs of \$26,000 with IVCF placement, due to the filter implantation procedure but more importantly to complications associated with its placement. Some of the complications associated with IVCF placement described are occlusion or perforation of the filter,(44) structural fracture, thrombosis, and migration of the IVCF (with risk of cardiac injury), perforation of the inferior vena cava and infection of the IVCF placement site.(5, 8, 14, 49) Immediate complications can also arise when the interventional radiologist, interventional cardiologist or vascular surgeon is placing the IVCF, such as misplacement, haematoma, air embolism, carotid artery puncture, arteriovenous fistula and pneumothorax.(8) The most serious complications usually arise in patients with prolonged exposure to the filter, so it is recommended to retrieve the filter as soon as possible,(44, 49) normally within 3 months.(8) The patient should also be advised to stop smoking at least until the IVCF is removed, as smoking is an extra risk factor for VTE.(8)

Apart from the risk of complications, IVCF placement also has some absolute contraindications (chronic complete thrombosis of the inferior vena cava and absence of access to the central vein) and relative contraindications (coagulopathy refractory to treatment, bacteraemia or sepsis and paediatric patients) that must be taken into account.(8)

In brief, while there are no randomized controlled trials,(4, 32, 44) the use of IVCF must be weighed up very carefully, attending to the individual risk of each patient, so that risk of VTE, haemorrhagic risk and risk of complications associated with IVCF may be balanced.

### **3.5.7. Other recommendations**

According to the AACE/TOS/ASMBS/OMA/ASA guidelines(1), oestrogen therapy should be stopped before bariatric surgery with the aim of reducing the risk of VTE. In the case of premenopausal women, they should discontinue one cycle of oral contraceptives while in the case of postmenopausal women, they must interrupt 3 weeks of hormone replacement therapy. Care should be taken to replace the contraceptive method with a non-oral contraceptive, since female patients must prevent pregnancy preoperatively and within 12 to 18 months postoperatively.(1)

### **3.6. Long term impact of bariatric surgery in the VTE risk**

The negative impact of bariatric surgery on the short-term risk of VTE (6-12 months postoperative) is described in several articles, but the positive long-term impact is rarely approached.(7, 9)

Obesity is a major predisposing factor for the occurrence of VTE, but it is also a reversible factor. Samuels et al.(34) showed that with weight loss, the hypercoagulability profile of patients with obesity improves, although it does not reach the results of healthy controls. One can easily conclude that if the BMI decreases, there is an improvement of the hypercoagulable profile and the risk of VTE decreases in a proportional way. Accordingly, any action that results in a lower BMI is beneficial in terms of thromboembolic risk, including bariatric surgery.(7, 9) . Bariatric surgery leads to significant weight loss which occurs up to 3 years postoperatively, a finding that supports VTE risk reduction in long term. Moussa et al.(7) observed that, 10.7 years after surgery, the long-term benefit of VTE risk reduction outweighs the short-term damage. However, it was noted that the risk of PE had remained unchanged.(7)

Overall, it can be understood that despite the increased short-term risk of VTE with bariatric surgery, the long-term benefits ultimately outweigh everything.

## **4. Conclusion**

VTE continues to be a reason for concern after bariatric surgery, even with prophylaxis use. Most studies are retrospective and observational, presenting some limitations, which results in wide heterogeneity of results, making it challenging to establish an optimal prophylaxis plan. Furthermore, it is unlikely that there is only one optimal prophylactic regimen for the entire

bariatric population. The ideal prophylactic plan must initially go through a careful evaluation of the individual risk factors for each patient. The most recent guidelines recommend the use of VTE risk calculators to divide patients into risk classes. Risk calculators have been developed specifically for bariatric surgery, but they have not yet been validated. Based on the score assigned to each patient it is possible to stratify into VTE risk classes, that crossed with the patient's haemorrhagic risk, it becomes possible to obtain not only the most effective prophylaxis but also the safest one. Regarding the different types of prophylaxis available, it was possible to determine an evident benefit of early ambulation as well as the use of mechanical prophylaxis or even measures such as the positioning of the patient on the operating table. When it comes to pharmacological prophylaxis, there is no doubt about its applicability and effectiveness, but there is still some work to be done. No consensus has been reached about the dose of drugs, initiation time, and duration of prophylaxis, which reflects the great need for large randomized controlled trials in patients with obesity undergoing bariatric surgery. With respect to the use of IVCF, this should be a last resort, only in very selected high-risk patients, where all risks of VTE, haemorrhage and complications should be considered.

Despite all this risk of complications that patients with obesity undergo with bariatric surgery, in the long term the benefits outweigh the harm, which is why it remains a popular approach to the treatment of severe obesity.

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