Venous Thromboembolism Prophylaxis and Treatment Protocol in Adults

1. Protocol Synopsis

Overview	This is an adapted evidence-based clinical practice protocol for the prediction, prevention, and management of VTE in Adults
Protocol Adapter	This protocol has been adapted by the Egyptian Society of Surgeons
Release Date	September 2021
Version	1.0
Scope and Purpose	This protocol covers assessing and reducing the risk of Venous Thromboembolism (VTE) in adult people. It aims to help healthcare professionals identify people at most risk and describe interventions that can be used to prevent and treat VTE. It doesn't cover children or young people aged under 18 years. It aims to maintain consistency of care, minimize variation in practice, improve patient outcomes and reduce morbidity and mortality due to VTE. It aims also to put clinical standards upon which the quality of care can be measured.
Target Users	This protocol is intended to be used by healthcare professionals who work as surgeons in different surgical specialties, internists in different specialties, obstetricians, gynecologists and other physicians caring for people at high risk for developing or having VTE.
Protocol Adaptation Methodology	This protocol was produced in accordance with ADAPTE methodology and procedure for the adaptation of evidence based clinical practice guidelines published by the ADAPTE group.
Sources of the Protocol	• ASH Updated Recommendations for Management of VTE (2020)

	• ASCO Guidelines for Prevention and Treatment of VTE in Cancer Patients (2020)[62] • ASH Guidelines for Diagnosis of VTE (2018)[60] • ASH Guidelines for Optimal Management of Anticoagulation Therapy for VTE (2021)[61] • ACCP Guidelines for Prevention and Treatment of Thrombosis (2021)[59] • AAOS Guidelines for Prevention of VTE in Hip and Knee Arthroplasty (2011)[63] • Adapted Egyptian Clinical Practice Guidelines on the Management of Venous Thrombosis (2021) • Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline. (2018)[64] • (ESVS) Clinical Practice Guidelines on the Management of Venous Thrombosis. (2021)[65] • RCOG Green-top Guideline No. 37a (2015)[66] • RCOG Green-top Guideline No. 37b (2015)[67]
Protocol Adaptation Team	

2. Amendment History

Document Version and Date	Revisions
Version 1, Dated September 2021	No Revisions. First Document Released.

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3. Introduction

3.1 Background:

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are two connected disorders that are part of the same spectrum and are both encompassed by Venous thromboembolism (VTE).[1] DVT is a major cause of morbidity and mortality among postoperative patients. Its incidence has been reported to range between 16% and 38% among general surgery patients.[2] PE occurs when a thrombus embedded in a pulmonary vessel blocks blood flow to one or more arteries of the lung. Both PE and DVT can occur as a result of disease processes, after major surgery or after hospitalization due to serious illness.[2]
After cardiac ischemic syndromes and stroke, Thromboembolic disease is the third most frequent acute cardiovascular condition.[3] The disease spectrum varies from clinically unsuspected to clinically unimportant to massive embolism resulting in death, and DVT and PE are frequently undiagnosed due to lack of clinical suspicion. Clinical PE occurs in 33-50 percent of patients with untreated acute proximal DVT.[4]
PE is usually recurrent over days to weeks if left untreated, and it can either improve on its own or result in death.[5]

3.2 Epidemiology

Egyptian statistics
More than one-third of all patients hospitalized for surgery or acute medical diseases are at high risk for developing VTE, according to a study by Goubran et al. conducted on ten Egyptian hospitals enrolling all surgical and medical patients. Only a small percentage (32.75%) of these patients, however, get effective VTE prophylaxis.[6]
International statistics
Internationally, thromboembolism has a major effect on morbidity and mortality. The total number of symptomatic, nonfatal VTE events each year was projected to be more than 295,000 cases of PE and more than 465,000 cases of DVT, according to a multinational report of European Union countries. More than 370,000 VTE-related deaths were calculated by the authors, of which only 7% were diagnosed before death and 34% being sudden fatal PE.[7]

3.3 Pathophysiology

Within a blood vessel, a thrombus is a solid mass of platelets and fibrin with few trapped red and white blood cells. A thrombus forms in the deep veins of the legs, pelvis, or arms due to hypercoagulability or blockage. Proximal extension happens as the clot expands, which might cause it to fragment or dislodge, and embolize the pulmonary arteries. Which leads to the obstruction of the pulmonary artery, and the sequential release of vasoactive substances (such as serotonin) by platelets resulting in an increase in pulmonary vascular resistance.
Due to the development of low ventilation-perfusion zones inside the lung, as a result of arterial blockage increasing alveolar dead space and causing blood flow redistribution, gas exchange impairment occurs.

Alveolar hyperventilation occurs when irritant receptors are stimulated. Airway resistance is increased as a result of reflex bronchoconstriction. Pulmonary compliance is reduced by the formation of lung edema. Increased pulmonary vascular resistance raises right ventricular afterload and tension in the right ventricular wall, potentially leading to right ventricular dilation, dysfunction, and ischemia.
Right heart failure can develop, resulting in cardiogenic shock and may even lead to death. Paradoxical embolism, as well as right-to-left shunting of blood with severe hypoxemia, can develop in the presence of a patent foramen ovale or atrial septal defect.

4. Risk Assessment of VTE

Patient-related factors, surgical factors, disease stages, and hematologic disorders are all risk factors for thromboembolic disease. The risk is additive.[17]
Age over 40, varicose veins, obesity, taking estrogen in pharmacologic doses (ie, oral contraceptives or hormone replacement therapy), and immobility are all patient-related factors.
Thromboembolic disease is more prevalent in patients with cancer, congestive heart failure, recent myocardial infarction, nephrotic syndrome, inflammatory bowel disease IBD, spinal cord injury with paralysis, and pelvic, hip, or long-bone fractures.[18]
Surgical factors are influenced by the type and duration of surgery. For example, A proximal DVT on the same side as the hip surgery affects about half of the patients who have had hip surgery.
According to one study, the following risk variables are significant indicators of VTE among hospitalized patients [19]:

- ⇒ Prior history of Venous thromboembolism[17]
- ⇒ Bed rest and prolonged immobility Previous VTE[16]
- ⇒ Cancer [20]
- ⇒ A Central venous catheterization line inserted peripherally[21]

The Kucher Score, a risk assessment score, was less successful than this four-element risk assessment model in identifying individuals at risk of VTE within 90 days.[22]
The following hematologic disorders increase the risk of thromboembolism[18]:

- ⇒ Antithrombin III deficiency
- ⇒ Lupus anticoagulant
- ⇒ Polycythemia vera
- ⇒ Paroxysmal nocturnal hemoglobinuria
- ⇒ Dysfibrinogenemia
- ⇒ Prothrombin mutation
- ⇒ Activated protein C resistance (factor V Leiden)
- ⇒ Protein C or protein S deficiency

4.1 Risk prediction algorithm

The Caprini RAM is a dynamic tool, requiring ongoing evaluation of the patient during their hospital course and the postoperative recovery period. Changes in clinical status could result in a change in the score, thereby resulting in a new score and potentially a revised treatment option. The 2013 Caprini scoring system provides a consistent, accurate, and efficacious method for risk stratification and selection of prophylaxis. (See Appendix A)

5. Prophylaxis

Pharmacologic Prophylaxis:

⇒ Medical prophylaxis should begin 12 hours prior to surgery or immediately afterwards, and must be continuous 7-10 days[23]

⇒ UFH administered subcutaneously can lower the risk of thromboembolism. [24]

⇒ A short-term course of thromboprophylaxis with the anticoagulant enoxaparin was found to be more effective than an extended course of another anticoagulant, apixaban, with considerably fewer serious bleeding events, according to data from an international, multicenter, randomized, controlled research. [25]

⇒ Warfarin is an efficient thromboprophylaxis treatment because it depletes vitamin K–dependent coagulation factors.[28] Warfarin must be closely monitored, and bleeding might occur as a complication. The INR should be kept in the range of 2.0-3.0 while using dose-adjusted treatment.[29]

Nonpharmacologic prophylaxis

⇒ It has been demonstrated that external pneumatic compression can counteract the decrease in fibrinolytic activity that occurs after surgery. [33]

⇒ Compression devices have been proven to be useful only in patients with head injuries or spinal fractures, however they have been demonstrated to be effective in reducing distal DVT only but not proximal DVT in total hip replacement patients.[34] Early ambulation, provided the patient does not have an absolute contraindication, is another type of nonpharmacologic prevention.[35] Studies have shown that both symptomatic DVT and DVT diagnosed ultrasonographically are much less common with early ambulation following hip arthroplasty.[36]

VTE Prophylaxis Hospital Policy

POLICY:

The hospital is committed to protecting patients through assessing all inpatients after 24 hours of admission in order to prevent deep vein thrombosis and lung clots formation by implementing the most updated treatment protocols.[31]

PURPOSE:

The policy's purpose is to give the hospital's staff clear directions on VTE risk assessment and prophylaxis for patients, as well as to ensure that appropriate measures are implemented to prevent VTE.

DEFINITIONS

Venous Thromboembolism (VTE): The formation of a blood clot (thrombus) in a vein that might dislodge from its original site of formation, resulting in an embolism.

VTE prophylaxis: The active mechanism that helps in minimizing the risk of a VTE.

⇒ Graduated compression stockings, venous foot pumps, and intermittent pneumatic compression, are examples of mechanical thromboprophylaxis devices. All of these treatments enhance venous outflow or decrease stasis in the leg veins.

⇒ Pharmacological thromboprophylaxis is a pharmaceutical treatment that reduces the blood's tendency to clot. Prescriptions will be written in accordance with the most recent version of the hospital formulary.

AFFECTED DEPARTMENTS:

Clinical pharmacists, Surgical and medical departments all departments that comply with the policies.

PROCEDURE:

1. Within 24 hours after admission, the primary registrar of each specialty is responsible for evaluating all patients and identifying patients at risk of venous thrombosis.

2. The evaluation is recorded in the "VTE risk assessment form" and filed in the medical records file.

3. Unless there are documented contraindications, all patients will be prescribed VTE prophylaxis according to hospital-approved protocol based on the patient's degree of VTE risk as reported on the VTE risk assessment tool.

4. In case of any variation from the hospital-approved protocol for VTE prophylaxis, a documentation of reasoning must be recorded in the patient's medical record.

5. In circumstances where VTE prophylaxis is contraindicated:
   ⇒ In the medical record, all contraindications to VTE prophylaxis must be documented.
   ⇒ Alternative mechanical approaches (e.g., sequential compression devices) will be used if VTE Pharmacologicalis contraindicated.
   ⇒ At 24–48-hour intervals, contraindications will be re-evaluated, with documentation of whether the contraindication is still persistent and whether the risk of VTE prophylaxis outweighs the risk of the identified contraindication.
6. Patients in critical care regions have their VTE risk monitored every 24 hours, and patients in non-critical care areas have their VTE risk examined every 48 hours.
7. If a dose cannot be administered as ordered, the reason must be recorded on Clinisys.
8. If a patient refuses prophylaxis, the registrar should provide patient education. When a patient is unable or unwilling to take a recommended Pharmacological

or mechanical device, the physician should be notified immediately so that alternate approaches may be investigated

8.1. Patient education includes:

8.1.1. The justification for the intervention(s)

8.1.2. The necessity for several intervention strategies such as sequential compression devices, heparin, etc. in order to reduce VTE risk

9. The attending physician for these patients' groups are as follow:
   9.1. VTE prophylaxis in critical care for Patients in ICUs
   9.2. VTE prophylaxis in surgery, for patients undergoing surgeries
   9.3. VTE prophylaxis in pediatric, for children aged between 12 and 18 years

10. Following the initial assessment, the attending physician sets a treatment plan to avoid strokes based on the VTE Prophylaxis protocol for all positive VTE patients.
11. The Clinical Pharmacist evaluates the VTE treatment protocol and makes recommendations.
12. The clinical pharmacist meets with the attending physician to discuss his recommendations and construct the final VTE strategy, which is then included in the patient's medical record.
13. The attending physician and clinical pharmacist assess the patient's reaction to the VTE plan.
14. Attending Physician records the patient's progress in the medical records

5.1 Multimodal prophylaxis

The following are commonly included in the multimodal VTE prophylaxis[32]:

- ⇒ Procoagulant medication discontinuation
- ⇒ VTE risk assessment
- ⇒ Regional anesthesia
- ⇒ Unfractionated Heparin IV bolus is administered before femoral preparation
- ⇒ Quick mobilization
- ⇒ Use of pneumatic compression devices
- ⇒ Pharmacologicaladjusted to the patient's VTE risk

Prophylaxis in Special Situations

- **VTE Prophylaxis in the most common vascular procedures**

The best perioperative precaution for patients having vascular surgery procedures is centered around striking a balance between the patient's thromboembolic risk and the procedure's bleeding risk. A general anticoagulant management strategy must be defined for each patient before the procedure, through the evaluation and risk-stratification of both surgical and patient-related risk factors of bleeding and thrombosis.

- **Patient's risk assessment for Venous Thrombosis:**

Vascular surgery encompasses a diverse set of procedures with varying levels of bleeding risk (Table 1). High bleeding risk is associated with open abdominal or thoracic aortic surgery for aneurysm or occlusive disease. Endovascular aneurysm repair and carotid endarterectomy, as well as endovascular procedures requiring a sheath greater than 8F, are considered intermediate risk, while endovascular procedures requiring smaller than 8F sheath or venous ablation are considered low risk. [37]

Table 1. Vascular procedures and associated procedural bleed risk.

Before starting VTE prophylaxis, patients should be evaluated for the risk of thromboembolism. The choice to begin VTE prophylaxis should be based on the patient's personal risk of thrombosis and bleeding, as well as the benefits vs risks balance. Although there are many tools for assessing thromboembolism risk, we recommend Caprini's Risk Assessment Model and Score for making decisions regarding the necessity for prophylaxis and classifying patients into four risk groups with appropriate prophylaxis measures based on both bleeding risk and patient assessment.[38]

*For patients undergoing cardiac or major vascular procedures, the ASH guideline panel recommends using pharmacological prophylaxis or no pharmacological prophylaxis[39]
**When pharmacological prophylaxis is used, the panel recommends using LMWH or UFH [39]

- ***Open vascular surgery or endovascular aneurysm repair*:**
  - ⇒ Consider pharmacological VTE prophylaxis with LMWH for at least 7 days for patients having open vascular surgery or major endovascular surgeries, such as endovascular aneurysm repair, where the risk of VTE outweighs risk of bleeding. [50]
  - ⇒ If Pharmacologicalis contraindicated then consider mechanical VTE prophylaxis (such as anti-embolism stockings or intermittent pneumatic compression) for patients undergoing open vascular surgery or major endovascular procedures, including endovascular aneurysm repair.[32]

- ***Lower limb amputation:***
  - ⇒ Consider pharmacological VTE prophylaxis with LMWH for at least 7 days if the risk of VTE exceeds the risk of bleeding in patients who are having a lower limb amputation. [41]
  - ⇒ if pharmacological prophylaxis is contraindicated consider mechanical VTE prevention with intermittent pneumatic compression on the contralateral leg on admission for patients who are having lower limb amputation procedure. [42]
  - ⇒ Continue mechanical VTE prophylaxis for patients who are having lower limb amputations until the patient's mobility is no longer considerably impaired compared to their expected mobility.

- ***Varicose vein surgery***
  - ⇒ VTE prophylaxis is usually not required for persons having varicose vein surgery if the total anesthetic duration is shorter than 90 minutes and the patient has a minimal risk of VTE.[43]
  - ⇒ If the total anesthesia period is more than 90 minutes or the patient's risk of VTE outweighs their risk of bleeding, consider pharmacological VTE prophylaxis with LMWH, commencing 6 to 12 hours after surgery and continuing for 7 days for patients undergoing varicose vein surgery.[44]
  - ⇒ . If pharmacological prophylaxis is contraindicated, consider mechanical VTE prophylaxis using anti-embolism stockings on admission for patients undergoing varicose vein surgery who are at increased risk of VTE.[45]
  - ⇒ Continue using anti-embolism stockings for patients having varicose vein surgery until their mobility is no longer considerably impaired compared to their expected mobility.

- **Prophylaxis in Cancer Patients**

  - ⇒ In the absence of bleeding or other contraindications, pharmacologic thromboprophylaxis should be administered to hospitalized patients with active malignancy, acute medical condition, or restricted mobility.[46]
  - ⇒ In the absence of bleeding or other contraindications, hospitalized patients with active malignancy and no extra risk factors may be given pharmaceutical thromboprophylaxis.[46]
  - ⇒ Patients hospitalized for minor surgeries or chemotherapy infusions, as well as patients undergoing stem-cell/bone marrow transplantation, should not receive routine pharmacologic thromboprophylaxis.[46]
  - ⇒ All outpatients with cancer cannot receive routine pharmacologic thromboprophylaxis..[47]
  - ⇒ If there are no significant risk factors for bleeding and no drug interactions, high-risk outpatients with cancer (Khorana score of 2 or higher prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH). In this situation, considering such medication should be accompanied by a discussion with the patient regarding the relative advantages and risks, cost of treatment, and the duration of prophylaxis.[48]

- ⇒ Unless contraindicated due to active bleeding, significant bleeding risk, or other limitations, all patients with malignant disease having major surgical intervention should be administered pharmacologic thromboprophylaxis with either unfractionated heparin (UFH) or LMWH.[50]
- ⇒ Mechanical approaches can be used in conjunction with pharmacologic thromboprophylaxis, but they should not be used alone to prevent VTE unless pharmacologic methods are contraindicated due to active bleeding or a significant risk of bleeding[46]
- ⇒ A combined pharmacologic and mechanical prophylactic treatment, especially in high-risk patients, may improve efficacy. For patients undergoing significant cancer surgery, pharmacologic thromboprophylaxis should be administered for at least 7-10 days.[51] For patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high-risk features such as restricted mobility, obesity, a history of VTE, or additional risk factors, extended prophylaxis with LMWH for up to 4 weeks postoperatively is suggested. In lower-risk surgical situations, the length of thromboprophylaxis should be determined on a case-by-case basis.[52]

⇒ ***VTE in Orthopedic surgery***

⇒ The risk of postoperative venous thromboembolism in orthopedic patients is among the highest of all surgical specialties .Assessing the risk of thrombosis — At baseline, select orthopedic surgeries are considered high risk (hip and knee arthroplasty, hip fracture surgery, pelvic and multiple fractures) and low risk (foot and ankle fractures; tibial, shoulder and elbow surgery; arthroscopy) for VTE with further stratification necessary according to the presence of additional patient- or procedure-related factors. Although the Caprini score can be used to stratify the risk of VTE, the score was validated in patients undergoing non-orthopedic surgery. [68]

- ⇒ VTE prophylaxis methods are divided into mechanical and pharmacological. The former include mobilization, gradu¬ated compression stockings, intermittent pneumatic com¬pression device and venous foot pumps; the latter include aspirin, unfractionated heparin, low molecular weight heparin (LMWH), adjusted dose vitamin K antagonists, syn¬thetic pentasaccharid factor Xa inhibitor (fondaparinux) and newer oral anticoagulants. LMWH seems to be more efficient overall compared with the other available agents. [69]
- ⇒ For patients undergoing THR or TKR, current ACCP guidelines recommend the use of LMWH, low-dose UFH, VKA, fondaparinux, apixaban, dabigatran, rivaroxaban, aspirin (all Grade 1B) or IPCD (Grade 1C) for at least 10 to 14 days and up to 35 days. The use of LMWH is suggested in preference to the other recommended agents (Grade 2B and 2C when it comes to adjusted-dose VKA or aspirin). When LMWH is used for VTE prophylaxis in patients undergoing THR or TKR, the administration is recommended to start either 12 hours or more pre-operatively or 12 hours or more post-operatively, rather than within 4 hours or less pre-operatively or 4 hours or less post-operatively.
- ⇒ For patients undergoing hip fracture repair, the ASH guideline [70] panel suggests using pharmacological prophylaxis over no pharmacological prophylaxis and

suggests using LMWH or UFH (unfractionated heparin](3). The duration of treatment is for at least 10 to 14 days and up to 35 days.

⇒ The reported incidence of DVT without prophylaxis after knee arthroscopy varies from 0.2% to 18% and consensus on VTE prophylaxis after knee arthroscopy has not been reached. Venous thromboembolism risk assessment should be a routine part of preoperative evaluation before Arthroscopic knee surgery , especially in high-risk patients older than 40 years [71].

⇒ For patients undergoing spine surgery who have addi¬tional VTE risk factors such as advanced age, malignancy, presence of neurologic deficits, history of VTE or an ante¬rior surgical approach, ACCP guidelines recommend that one of the following VTE prophylaxis options be used: post-operative low-dose UFH (Grade 1B); post-operative LMWH (Grade 1B); or optimal use of peri-operative IPC (Grade 1B) or GCS (Grade 2B) as an alternative. For patients undergoing spine surgery who have multiple risk factors for VTE, the combination of a pharmacologic method with the optimal use of a mechanical method is recommended (Grade 2C). For all patients with acute SCI it is recommended that routine VTE prophylaxis should be administered (Grade 1A); in these patients, VTE prophylaxis with LMWH is recommended to commence once primary haemostasis is evident (Grade 1B).

⇒ The incidence of DVT following short leg cast immobilization is in the range of 4% to > 16%. A 2014 meta-analysis showed a 4.3% to 40% incidence of DVT after casting and recommended the use of LMWH for all patients undergoing casting[72].

⇒ Aspirin (acetylsalicylic acid) is an inexpensive, orally administered and widely available medication with a con-troversial use as a prophylactic agent for VTE[71]. Overall, it seems that the use of aspirin as a VTE prophy¬laxis agent in orthopaedic patients remains controversial. A recent review of the use of aspirin after THA and TKA also concludes that, for appropriately selected low-risk patients, aspirin following rivaroxaban (as performed in a recent randomized trial [70,73] is likely safe and effective. According to a meta-analysis in 2016, although aspirin is a suitable therapy for the prevention of VTE in THR and TKR, as recommended by the ACCP and AAOS, the evidence available is of limited quality and still remains unclear about the dosage and duration of administration of aspi¬rin for VTE prophylaxis [74].

6. Recommendations for Pregnancy and Puerperium

⇒ All women should undergo a documented assessment of risk factors for VTE in early pregnancy or prepregnancy.[66]

⇒ Risk assessment should be repeated if the woman is admitted to hospital for any reason or develops other intercurrent problems. [66]

⇒ Risk assessment should be repeated again intrapartum or immediately postpartum. [66]

⇒ Any woman with four or more current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic low-molecular-weight heparin (LMWH) throughout the antenatal period and will

usually require prophylactic LMWH for 6 weeks postnatally but a postnatal risk reassessment should be made. [66]

⇒ Any woman with three current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH from 28 weeks and will usually require prophylactic LMWH for 6 weeks postnatally but a postnatal risk reassessment should be made. [66]

⇒ Any woman with two current risk factors shown in Appendix I and Table 1 (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH for at least 10 days postpartum. [66]

⇒ Women admitted to hospital when pregnant (including to the gynaecology ward with hyperemesis gravidarum or ovarian hyperstimulation syndrome) should usually be offered thromboprophylaxis with LMWH unless there is a specific contraindication such as risk of labour or active bleeding. [66]

⇒ The risk of VTE should be discussed with women at risk and the reasons for individual recommendations explained. [66]

⇒ Women with previous VTE associated with antithrombin deficiency (who will often be on long-term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery.

⇒ Management should be undertaken in collaboration with a haematologist with expertise in thrombosis in pregnancy and consideration given to antenatal anti-Xa monitoring and the potential for antithrombin replacement at initiation of labour or prior to caesarean section. [66]

⇒ If anti-Xa levels are measured, a test that does not use exogenous antithrombin should be used and 4-hour peak levels of 0.5–1.0 iu/ml aimed for. [66]

⇒ Other heritable thrombophilic defects are lower risk and can be managed with standard doses of thromboprophylaxis. [66]

⇒ Women with VTE associated with the antiphospholipid syndrome (APS) (who will often be on long- term oral anticoagulation) should be offered thromboprophylaxis with higher dose LMWH (either 50%, 75% or full treatment dose) (see Appendix IV) antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery. [66]

⇒ Pregnant women with APS and prior VTE or arterial thromboses should be managed in collaboration with a haematologist and/or rheumatologist with expertise in this area. [66]

7. Surgery

General surgery

Deep venous thrombosis (DVT) is a major cause of morbidity and mortality among postoperative patients. Its incidence has been reported to range between 16% and 38% among general surgery patients. During the acute phase of DVT, 10 to 40% of patients may develop PE (Pulmonary Embolism), having a mortality rate as high as 10 to 20%. However, the mortality rate for PE has been stated to be as high as 30% in studies that included autopsy-based diagnosis of PE.

Recommendations for Colorectal surgery and DVT

Compared to general surgery, colorectal surgery is associated with a higher risk for postoperative deep venous thrombosis (DVT) and pulmonary embolism (PE). Among colorectal conditions, colorectal cancer (CRC) and inflammatory bowel disease (IBD) are well-known risk factors for venous thromboembolism (VTE), with an estimated incidence of VTE of 2.75%–8.9% among patients with CRC.
The high risk of VTE in colorectal surgery is thought to be associated with
1-Pelvic dissection
2-Patient positioning
3-Malignancey
4-Increasing age

The presence of these risk factors places colorectal cancer surgery patients at an increased risk of VTE compared to general surgical patients

The risk of VTE in colorectal surgery is not insignificant, and therefore, patients should be offered appropriate prophylaxis in order to reduce the risk of perioperative VTE. Patients undergoing colorectal surgery should be carefully stratified according to their VTE risk, taking into account risk factors.

Recommendations for Bariatric surgery and DVT

Patients undergoing bariatric surgery are at an increased risk for venous thromboembolism. The incidence of symptomatic deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients following bariatric surgery ranges from 0 to 5.4 percent and 0 to 6.4 percent, respectively. with the majority occurring following discharge from the hospital within 30 days.

Risk of bariatric surgery:
1)The positive pressure during laparoscopic inflation has been associated with oxidative stress during surgery which, in turn, will cause endothelial dysfunction and platelet aggregation.
2)The position of the patient, tilted feet down to 15°, as well as the duration of the operation, both contribute to decreased blood flow. The duration is influenced by the type of surgery performed.
3)Hypercoagulability because of abnormal fibrinogen concentration, increased plasminogen activator inhibitor 1 (PAI-1), and reduced antithrombin III and fibrinolysis.

4)Moreover, venous hemodynamics are affected by obesity; dilatation and reduced venous flow were reported in lower limbs using color-coded duplex ultrasound.
N.B.: In bariatric surgery most patients need to continue with anticoagulation for 7–21 days depending of individual risk assessment.

8. Treatment of VTE

Initial management:

- **Home treatment:**

⇒ **For patients with uncomplicated deep vein thrombosis (DVT), the American Society of Hematology (ASH) guideline panel suggests offering home treatment over hospital treatment.**

⇒ **Also, ESVS recommends outpatient treatment for VTE (IA.)**

⇒ **For patients with pulmonary embolism (PE) with a low risk for complications, the ASH guideline panel suggests offering home treatment over hospital treatment**

Patient ambulation:

In patients with acute DVT of the leg, ACCP suggests early ambulation over initial bed rest (Grade 2C)

Anticoagulation therapy for the treatment of deep vein thrombosis:

⇒ **Traditionally** The treatment of DVT has been dominated using IV UFH or subcutaneous LMWH for the initial acute phase (up to 10 days), followed by a VKA such as warfarin, or LMWH for the principal phase of treatment (three months).

⇒ The use of DOACs was a major advance in the treatment of DVT as these medications have a similar efficacy to and a better safety profile than VKAs

⇒ All these drugs have a similar efficacy in the treatment of acute symptomatic VTE, with a significant reduction in the risk of major bleeding in both provoked and unprovoked DVT.

For patients with DVT and/or PE, the ASH guideline panel suggests using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs)

Anticoagulation therapy for the treatment of provoked deep vein thrombosis:

⇒ Provoking factors for DVT can be transient (such as surgery or hospital admission with bed rest [strict or with bathroom privileges] lasting at least three days) or persistent (such as thrombophilia) and may be associated with varying risks of DVT recurrence, Treatment options for cancer associated venous thrombosis (CAVT).

⇒ The introduction of DOACs is the recommended first line treatment for DVT of lower limb.

⇒ Direct oral anticoagulants (DOACs) such as dabigatran, Apixaban, edoxaban, and rivaroxaban are direct oral anticoagulants that directly inhibit factor Xa and they don't require parenteral initial dose to be effective, but Dabigatran is administered at a dose of 150 mg twice per day, which is started after at least five days of initial

parenteral anticoagulation until it's activated in plasma, and also Edoxaban, like dabigatran, requires at least five days of parenteral anticoagulation before starting oral dosing at 60 mg twice per day.

⇒ Direct oral anticoagulants (DOACs) such as dabigatran, Apixaban, edoxaban, and rivaroxaban are direct oral anticoagulants that directly inhibit factor Xa and they don't require parenteral initial dose to be effective, but Dabigatran is administered at a dose of 150 mg twice per day, which is started after at least five days of initial parenteral anticoagulation until it's activated in plasma, and also Edoxaban, like dabigatran, requires at least five days of parenteral anticoagulation before starting oral dosing at 60 mg twice per day.

⇒ **While Apixaban is started without initial parenteral therapy but requires a higher dose (10 mg twice per day) for seven days, followed by the standard treatment dose of 5 mg twice per day, and Rivaroxaban is started without initial parenteral therapy but requires a higher dose (15 mg twice per day) for three weeks, followed by the standard treatment dose of 20 mg once per day.**

⇒ **For patients with provoked proximal deep vein thrombosis, treatment with Direct Oral Anticoagulants is recommended over vit.A antagonists for the principal treatment phase. IA**

⇒ **For patients with unprovoked proximal deep vein thrombosis, treatment with Direct Oral Anticoagulants is recommended over Low Molecular Weight Heparin followed by vit.A antagonists for the principal treatment phase. IA**

<u>Duration of anticoagulation therapy</u>

⇒ The reduced dose of rivaroxaban and apixaban is also an option for most patients requiring extended treatment, with further reductions of bleeding without a compromise in their efficacy

⇒ The biological behavior of provoked DVT with persistent or transient minor risk factors is close to unprovoked DVT, so a strategy for extended anticoagulation like unprovoked DVT should be discussed with the patient.

⇒ **For patients with a provoked proximal deep vein thrombosis with a major transient risk factor, three months of anticoagulation treatment is recommended over a shorter duration. IA**

⇒ **In selected patients with provoked proximal deep vein thrombosis, with a persistent risk factor other than malignancy, anticoagulation beyond three months should be considered after evaluation of thrombotic and bleeding risks, with periodic reassessment. IIa**

⇒ **For patients with unprovoked deep vein thrombosis, reassessment of bleeding risk is recommended before continuing anticoagulation beyond three months.IC**

Strategies to reduce the risk of recurrence:

The likelihood of recurrent DVT after discontinuation of anticoagulation is high, particularly in patients with unprovoked DVT. For patients with provoked DVT, the overall recurrence rate after stopping anticoagulation is approximately half the rate for unprovoked DVT,157 but may be as high as the population with unprovoked DVT for patients with minor risk factors, and much lower in patients with major, transient provoking factors. Consequently, several strategies and clinical trials have been tested to reduce the risk. Unfractionated heparin, low molecular weight heparins, vitamin K antagonists, and direct oral anticoagulants. The wide range of anticoagulants now available allows individualized management of patients with DVT. Aspirin. Prior to the DOACs, aspirin was widely investigated for the prevention of recurrent VTE

- ⇒ **For patients with unprovoked proximal deep vein thrombosis requiring extended anticoagulation beyond six months but not deemed to be at very high risk of recurrence use of a reduced dose of the direct oral anticoagulants apixaban or rivaroxaban should be considered IIa**
- ⇒ **For patients with unprovoked deep vein thrombosis aspirin is not recommended for extended antithrombotic therapies. III**

Monitoring and surveillance after deep vein thrombosis

The Duration of Anticoagulation based on Compression Ultrasonography (DACUS) study, ultrasound was used to determine the presence of residual obstruction. The term residual vein thrombosis is used in the original publication, but residual venous obstruction (RVO) now is the preferred terminology. Residual obstruction was considered present if there was non-compressibility of 40% of the vein diameter. Patients with a first episode of DVT, treated by anticoagulation for three months, were managed according to the presence of RVO.

- ⇒ **For patients with deep vein thrombosis, repeat whole leg ultrasound may be considered at the end of anticoagulant treatment to determine the new baseline anatomic status. IIa**
- ⇒ **For patients with deep vein thrombosis, who are potential candidates for extended treatment, residual vein obstruction and/ or d-dimer level may be considered at the decision-making process. IIb**

Treatment of deep vein thrombosis: use of inferior vena cava filters:

- ⇒ It should be noted that the sole purpose of IVC filters is to prevent PE and therefore to reduce PE associated morbidity and mortality.
- ⇒ Nevertheless, IVC filters are the only viable treatment option for patients with DVT where anticoagulation is contra indicated, although randomized trials are urgently needed. Although an IVC filter is a possible means of minimizing major PE, it has no positive effect on the DVT itself**.**
- ⇒ **For patients who are anticoagulated for deep vein thrombosis, the routine use of inferior vena cava filters is not recommended. III**
- ⇒ **For patients with proximal deep vein thrombosis, who have contraindication for anticoagulation in the initial phase of the principal treatment; inferior vena cava**

filter is recommended.

Treatment of deep vein thrombosis using compression therapy

⇒ Compression therapy is a non-invasive treatment option, which is readily available and is associated with few complications. Contraindications to compression are limited to two categories of patients: patients with severe lower extremity arterial disease (ankle brachial index < 0.50 or absolute ankle pressure < 60 mmHg),178 and patients with severe congestive heart failure as there might be a risk of systemic fluid overload**.**

Treatment of deep vein thrombosis: early thrombus removal and stenting

The increasing recognition that after best executed anticoagulant management PTS develops in 25% e 75% of patients with extensive lower extremity DVT has inspired ongoing attempts at early thrombus removal. Research has clearly linked the development and progression of PTS to the persistence of venous thrombus and venous valvular injury that stems from the inflammatory reaction to this thrombus. There have been four RCTs (TORPEDO [Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion], CaVenT [Catheter- Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis], ATTRACT, and CAVA [CAtheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT]) examining the effectiveness of early thrombus removal strategies.

⇒ **In selected patients with symptomatic iliofemoral deep vein thrombosis, early thrombus removal strategies should be considered. IIa**

⇒ **For patients with deep vein thrombosis limited to femoral popliteal or calf veins, already thrombus removal is not recommended. III**

⇒ **For patients with deep vein thrombosis treated by early thrombus removal, with or without stenting, it is recommended that the duration of anticoagulation should be at least as long as if the patients were treated by anticoagulation alone and at the discretion of the treating physician. IC**

⇒ **For patients with iliofemoral deep vein thrombosis who undergo early thrombus remove moving it is recommended that the choice of therapy is based on the judgment of the treating physician. IIa**

Cancer associated deep vein thrombosis:

Although malignancy has been recognized as a risk factor for DVT for over a century, an increased risk of recurrent VTE during anticoagulant treatment in such patients vs. those without malignancy had not been described until relatively recently. A recent meta-analysis identified 23 RCTs with 6 980 patients.365 LMWHs were more effective than VKAs in preventing recurrent VTE (RR 0.58, 9CI 0.45 e 0.75) and DVT (RR 0.44, 95% CI 0.29 e 0.69). DOACs were more effective than VKAs in preventing recurrent VTE (RR 0.65, 95% CI 0.45 e 0.95), but equivalent regarding overall mortality or bleeding. However, anti-Xa DOACs were more effective than VKAs (RR for VTE 0.64, 95% CI 0.42 e 0.97) and caused less bleeding, although major bleeding was reduced only with DOACs no requiring initial parenteral anticoagulation with heparin, i.e., rivaroxaban and apixaban (RR 0.45, 95% CI 0.21 e 0.97).

⇒ **For patients with cancer associated deep vein thrombosis, hello molecular weight heparin is recommended for initial and principal phase anticoagulation. IA**

⇒ **In selected patients with cancer associated deep vein thrombosis, with the malignancy not located in the gastrointestinal or genitourinary systems and approved directorial anticoagulant for initial principle and extended treatment should be considered.**

IIa

⇒ **For patients with active cancer associated deep vein thrombosis switching from a low molecular weight heparin to an oral anticoagulant is recommended after three to six months of treatment for extended treatment.**

IC

9. Complications

Postthrombotic syndrome

Postthrombotic syndrome (postphlebitic syndrome), a chronic complication of VTE characterized by pain and swelling, is the most common long-term effect of treated DVT. In about 50% of patients treated with complete anticoagulation, chronic deep venous insufficiency, venous stasis, recurrent cellulitis, and skin ulceration can develop.[9]

Bleeding

Severe and even fatal bleeding is the most dreaded complication of PE treatment. Intensity and length of therapy, old age, and substantial hepatic or renal dysfunction are all major risk factors for bleeding. There have been no substantial differences in the incidence of serious and fatal bleeding complications between heparin and rt-PA, according to comparison studies. When severe bleeding occurs, treatment with agent-specific approaches may be necessary.[10]

Heparin-induced thrombocytopenia

In 3-4 percent of heparin-treated patients, heparin-induced thrombocytopenia (HIT) and thrombosis might occur.[11] It's an immune-mediated condition that usually shows up within 5-10 days of treatment. It can cause bleeding or thrombosis, and it should be anticipated if the platelet count drops to less than half of its baseline value or less than 100,000/µL. Heparin therapy must be terminated immediately in such cases.[11]

In 90 percent of cases, LMWH reacts with the antibody in vitro. As a result, it should not be used in acute cases. Danaparoid, which is a heparinoid, shows a cross-reactivity with the antibody of less than 10%.[12]

Fondaparinux has been used in the treatment of suspected HIT patients as anticoagulant with a lesser degree of HIT occurrence. Herodin, liprodin or linuax can be used [13]

Heparin-induced osteopenia

After more than a month of UFH treatment, heparin-induced osteopenia has been reported.[14]

Skin necrosis

As a result of widespread subcutaneous microthrombosis, coumarin derivatives can cause skin necrosis. This can develop in patients who are protein C–deficient, either genetically or as a result of high coumarin derivative loading dosages. Breasts, abdominal wall, and lower extremities are commonly afflicted. [15]

Recurrence

Following the discontinuation of medication, recurrence of thromboembolism was observed. Patients with reversible risk factors have a lesser risk of recurrent thromboembolism after a 3- to 6-month course of anticoagulant medication. Patients with previous proximal vein thrombosis have a higher recurrence risk than those with calf vein thrombosis.[16]

In the first year after a 3-month course of anticoagulant treatment, the risk of recurrent thrombosis is 2-4 percent. The risk of recurrence is depending on the triggering risk factor: if VTE is caused by surgery, the risk is low; if it is caused by a nonsurgical risk factor, the risk is intermediate; and if it is unprovoked and develops in a patient with disease-related risk factor, the risk is high.[16]

Appendix A: VTE Risk assessment Model for Adults

Risk Factors for Predicting VTE in Hospitalized Surgical Patients (Caprini Score)	
Each risk factor represents 1 points	Each risk factor represents 2 points
☐ Age 41 – 60 years ☐ Minor surgery planned ☐ Obesity (BMI > 25) ☐ Swollen legs (current) ☐ Varicose veins ☐ Pregnancy/Postpartum ☐ History of unexplained/recurrent spontaneous abortion ☐ Oral contraceptives/HRT ☐ History of prior major surgery (<1 month) ☐ Sepsis (< 1 month) ☐ Serious lung disease incl. pneumonia (<1 month) ☐ Abnormal pulmonary function (COPD) ☐ Acute myocardial infarction ☐ Congestive heart failure (< 1 month) ☐ History of inflammatory bowel disease ☐ Medical patient currently at bed rest	☐ Age 61- 74 years ☐ Arthroscopic surgery ☐ Major surgery (> 45 minutes) ☐ Laparoscopic surgery (> 45 minutes) ☐ Malignancy (present previous) ☐ Patient confined to bed (> 72hours) ☐ Immobilizing plaster cast (< 1 month) ☐ Central venous access
Each risk factor represents 3 points	Each risk factor represents 5 points
☐ Age ≥ 75 years ☐ History of VTE ☐ Family history of VTE ☐ Positive factor V Leiden ☐ Positive prothrombin 20210/A ☐ Positive lupus anticoagulant ☐ Elevated serum homocysteine ☐ Elevated anticardiolipin antibodies ☐ Heparin-induced thrombocytopenia (HIT) ☐ Other congenital or acquired thrombophilia	☐ Stroke (< 1 month) ☐ Elective major lower extremity arthroplasty ☐ Acute spinal cord injury (paralysis) (<1 month)

Risk score interpretation

Total Risk Score	Risk of VTE	Management
0	Very low	Early ambulation
1 – 2	Low	IPC
3 – 4	Moderate	Pharmacological, IPC
≥ 5	High	Pharmacological + GCS or IPC

Date/Time							
Score							
Physician signature							

Pharmacological agent Selection

- Enoxaparin 40 mg OD (PLT > 100 microL, CrCl > 30 ml/min & no history of HIT (increase by 30% if BMI ≥ 40Kg/m²)
- Enoxaparin 20-30 mg OD (PLt > 100/microL, 15 < CrCl < 30 ml/min. & no history of HIT)
- Enoxaparin 30 mg Q 12 hr (Knee replacement surgery).
- Heparin 5000 q 8–12 hrs (PLt > 100/microL, CrCl < 15 ml/min & no history of HIT)
- Fondaparinux 2.5 mg OD or Hirudin15 mg Q12 hr (PLT< 100/microL, HIT, CrCl > 30 ml/min. Wt > 50 kg).
- Warfarin; INR (2-3)
- Rivaroxaban; 10 mg OD
- Apixaban; 2.5 twice daily

GCS: Graduated Compression Stockings
IPC: Intermittent Pneumatic compression

Appendix B: VTE Risk Assessment in Cancer Outpatients

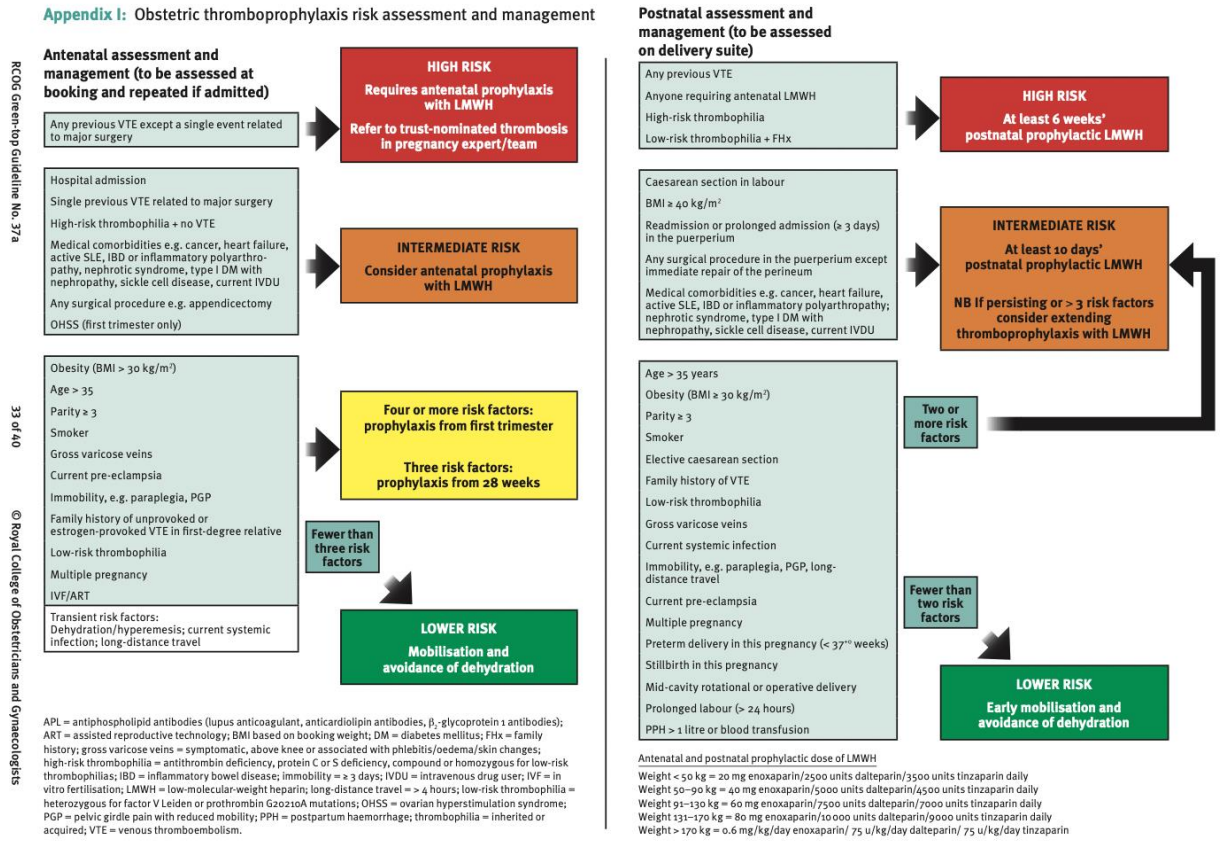
VTE RISK ASSESSMENT IN CANCER OUTPATIENTS

Khorana Predictive Model for Chemotherapy-Associated VTE[1]

Patient Characteristic	Risk Score
• Site of primary cancer	
◦ Very high risk (stomach, pancreas)	2
◦ High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
• Prechemotherapy platelet count 350 x 10^9/L or higher	1
• Hemoglobin level less than 10 g/dL or use of red cell growth factors	1
• Prechemotherapy leukocyte count higher than 11 x 10^9/L	1
• BMI 35 kg/m^2 or higher	1

Total Score	Risk Category	Risk of Symptomatic VTE[2]
0	Low	0.3–1.5%
1, 2	Intermediate	1.8–4.8%
3 or higher	High	6.7–12.9%

Appendix C: Obstetric Thromboprophylaxis Risk Assessment and Management (RCOG Green top)



Appendix D: Gynecology Risk Factors for VTE

Appendix III: Risk assessment for venous thromboembolism (VTE)

- If total score ≥ 4 antenatally, consider thromboprophylaxis from the first trimester.
- If total score 3 antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally consider thromboprophylaxis.
- If prolonged admission (≥ 3 days) or readmission to hospital within the puerperium consider thromboprophylaxis.

For patients with an identified bleeding risk, the balance of risks of bleeding and thrombosis should be discussed in consultation with a haematologist with expertise in thrombosis and bleeding in pregnancy.

Risk factors for VTE

Pre-existing risk factors	Tick	Score
Previous VTE (except a single event related to major surgery)		4
Previous VTE provoked by major surgery		3
Known high-risk thrombophilia		3
Medical comorbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user		3
Family history of unprovoked or estrogen-related VTE in first-degree relative		1
Known low-risk thrombophilia (no VTE)		1[a]
Age (> 35 years)		1
Obesity		1 or 2[b]
Parity ≥ 3		1
Smoker		1
Gross varicose veins		1
Obstetric risk factors		
Pre-eclampsia in current pregnancy		1
ART/IVF (antenatal only)		1
Multiple pregnancy		1
Caesarean section in labour		2
Elective caesarean section		1
Mid-cavity or rotational operative delivery		1
Prolonged labour (> 24 hours)		1
PPH (> 1 litre or transfusion)		1
Preterm birth < 37[+0] weeks in current pregnancy		1
Stillbirth in current pregnancy		1
Transient risk factors		
Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilisation		3
Hyperemesis		3
OHSS (first trimester only)		4
Current systemic infection		1
Immobility, dehydration		1
TOTAL		

Appendix E: VTE Bleed Risk Score Assessment

Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points
H	Hypertension (ie, uncontrolled blood pressure)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs (for patients taking warfarin)	1
E	Elderly (age greater than 65 years)	1
D	Drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1 point each)	1 or 2
		Maximum 9 points

HAS-BLED score (total points)	Bleeds per 100 patient-years ¶
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5 to 9	Insufficient data

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11. Summary

1. **For most patients with deep vein thrombosis, outpatient management is required**
2. **In patients with acute DVT of the leg, early ambulation over initial bed rest is suggested**
3. **For patients with provoked proximal deep vein thrombosis, treatment with a direct oral anticoagulant is recommended over a vitamin K antagonist for the principal treatment phase.**
4. **For patients with unprovoked proximal deep vein thrombosis, treatment with a direct oral anticoagulant is recommended over treatment with low molecular weight heparin followed by a vitamin K antagonist for the principal treatment phase.**
5. **For patients with a provoked proximal deep vein thrombosis with a major transient risk factor, three months of anticoagulation treatment is recommended over a shorter duration.**
6. **In selected patients with provoked proximal deep vein thrombosis, with a persistent risk factor other than malignancy, anticoagulation beyond three months should be considered after evaluation of thrombotic and bleeding risks, with periodic reassessment.**
7. **For patients with unprovoked deep vein thrombosis, reassessment of bleeding risk is recommended before continuing anticoagulation beyond three months**
8. **For patients with deep vein thrombosis, repeat whole leg ultrasound may be considered at the end of anticoagulant treatment to determine the new baseline anatomic status**
9. **For patients with unprovoked proximal deep vein thrombosis requiring extended anticoagulation beyond six months but not deemed to be at very high risk of recurrence use of a reduced dose of the direct oral anticoagulants apixaban or rivaroxaban should be considered**
10. **For patients with unprovoked deep vein thrombosis aspirin is not recommended for extended antithrombotic therapy**
11. **For patients who are anticoagulated for deep vein thrombosis, the routine use of inferior vena cava filters is not recommended**
12. **For patients with proximal deep vein thrombosis who have contraindications to anticoagulation during the initial or principal in treatment phase temporary inferior vena cava filter insertion is recommended**
13. **In selected patients with symptomatic iliofemoral deep vein thrombosis, early thrombus removal strategies should be considered**

14. **For patients with deep vein thrombosis limited to femoral popliteal or calf veins, already thrombus removal is not recommended**
15. **For patients with deep vein thrombosis treated by early thrombus removal, with or without stenting, it is recommended that the duration of anticoagulation should be at least as long as if the patients were treated by anticoagulation alone and at the discretion of the treating physician**
16. **For patients with iliofemoral deep vein thrombosis who undergo early thrombus remove moving it is recommended that the choice of therapy is based on the judgment of the treating physician**
17. **For patients with cancer associated deep vein thrombosis, hello molecular weight heparin is recommended for initial and principal phase anticoagulation**
18. **In selected patients with cancer associated deep vein thrombosis, with the malignancy not located in the gastrointestinal or genitourinary systems, and approved directorial anticoagulant for initial principle and extended treatment should be considered**
19. **For patients with active cancer associated deep vein thrombosis switching from a low molecular weight heparin to an oral anticoagulant is recommended after three to six months of treatment for extended treatment**
20. **Fondaparinux has been used in the treatment of suspected HIT patients as anticoagulant with a lesser degree of HIT occurrence. Herodin, liprodin or linuax can be used [13]**
21. **After more than a month of UFH treatment, heparin-induced osteopenia has been reported.[14]**
22. **The following are commonly included in the multimodal VTE prophylaxis[32] :**
    - ⇒ **Procoagulant medication discontinuation**
    - ⇒ **VTE risk assessment**
    - ⇒ **Regional anesthesia**
    - ⇒ **Unfractionated Heparin IV bolus is administered before femoral preparation**
    - ⇒ **Quick mobilization**
    - ⇒ **Use of pneumatic compression devices**
    - ⇒ **Pharmacologicaladjusted to the patient's VTE risk**

23. **In the absence of bleeding or other contraindications, pharmacologic thromboprophylaxis should be administered to hospitalized patients with active malignancy, acute medical condition, or restricted mobility.[46]**

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