BMJ Best Practice

VTE prophylaxis

The right clinical information, right where it's needed

Last updated: Dec 17, 2017

Table of Contents

Summary

- Thromboprophylaxis is the most important patient safety strategy in patients admitted to hospital. Pulmonary embolism (PE) remains the leading cause of preventable in-hospital death.
- The risk of venous thrombosis in patients admitted to hospital depends on medical versus surgical admission and, among surgical patients, the type of surgery.
- Evaluating venous thromboembolic risk factors within these patient groups helps further stratify the thrombotic risk.
- Bleeding risk and possible contraindication to anti-thrombotic agents must be assessed before instituting thromboprophylaxis.
- Although national and international thromboprophylaxis guidelines have repeatedly recommended thromboprophylaxis of patients admitted to hospital, only 40% to 50% of medical patients and 60% to 75% of surgical patients receive adequate thromboprophylaxis.
- Computer-based decision systems and pre-printed orders are most effective in optimising physician adherence to thromboprophylaxis guidelines. Periodic audits by pharmacists or other health professionals reinforce the consistent use of venous thromboembolism prophylaxis.

BASICS

Definition

Venous thromboembolism (VTE) prophylaxis consists of pharmacological and non-pharmacological measures to diminish the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE).

DVT of the leg is the development of a blood clot in one of the major deep veins in the leg or thigh, which leads to impaired venous blood flow, usually causing leg swelling and pain.

PE is a consequence of thrombus formation in distal veins, most commonly those of the deep venous system of the lower extremities. Thrombus formation in the venous system occurs as a result of venous stasis, trauma, and hypercoagulability. About 51% of deep venous thrombi will embolise to the pulmonary vasculature, resulting in a PE.[1]

Epidemiology

The US Agency for Healthcare Research and Quality (AHRQ) rates thromboprophylaxis the number one patient safety strategy for patients admitted to hospital.[2] Patients admitted to hospital are increasingly burdened with disease, and immobilisation contributes to making them prime candidates for development of VTE. Without prophylaxis, the incidence of symptomatic DVT acquired in hospital is about 10% to 20% in medical patients, 15% to 40% in general surgery patients, and 40% to 60% in major orthopaedic surgery patients.[3] [4] PE remains the most common cause of preventable in-hospital death in the US, according to the AHRQ.[2] Postoperative VTE was also the second most common cause of excess length of stay in hospital in a large US-based study.[5] Moreover, treatment of PE or DVT entails at least 3 months of anticoagulation with significant risk of bleeding.[3] Even with adequate anticoagulation, a significant proportion of patients develop long-term complications. About 3% of patients with PE develop chronic pulmonary hypertension, and 20% to 50% of patients with DVT develop post-phlebitic syndrome.[6] [7] [8] VTE prophylaxis consists of pharmacological and non-pharmacological measures to diminish the risk of DVT and PE.

Aetiology

Virchow's triad is still the preferred aetiological model for VTE.[9]

- Vessel wall damage: endothelial cell damage promotes thrombus formation, usually at the venous valves. Trauma, previous DVT, surgery, venous harvest, and central venous catheterisation can cause damage to the vessel wall.[10]
- Venous stasis: the formation of thrombi is promoted by poor blood flow and stasis. Venous stasis and congestion result in valvular damage, further promoting thrombus formation. The following factors increase the risk for venous stasis: age >40 years, immobility, general anaesthesia, paralysis, spinal cord injury, myocardial infarction, prior CVA, varicose veins, advanced CHF, and advanced COPD.
- Hypercoagulability: a number of other conditions (both inherited and acquired) increase the risk of VTE. These include cancer, high-oestrogen states (obesity, pregnancy, and hormone replacement), inflammatory bowel disease, nephrotic syndrome, sepsis, and inherited thrombophilias (factor V Leiden mutation, prothrombin gene mutation, protein C and S deficiency, anti-thrombin III deficiency, and anti-phospholipid antibody syndrome).

Pathophysiology

The most common initial site for thrombi forming in the deep venous system of the leg is just above and behind a venous valve.[11] [12] Thrombi do not develop de novo in the pulmonary vasculature. Usually, they resolve spontaneously. When a thrombus does propagate, it expands and grows in a proximal direction and across the lumen of the vein. In most cases, a small amount of flow continues on the extreme periphery of the thrombus, although complete obstruction can occur. Thrombi start in the calf veins and propagate in a proximal direction. However, in some instances, such as during pregnancy or following total hip arthroplasty, thrombus formation might initially be in the groin or iliac vein region. The pathophysiology of PE is therefore directly related to that of DVT. Endothelial damage appears to be less important in DVT than in arterial thrombosis.[13] PE occurs when a thrombus dislodges and becomes trapped in the pulmonary vasculature.[14]

Secondary prevention

Secondary prophylaxis refers to preventing VTE recurrence. When acute DVT or PE is diagnosed, anticoagulant therapy is prescribed not only to treat local symptoms such as pain and swelling and to prevent extension of the DVT and/or PE, but also to provide prophylaxis against recurrence (or secondary prophylaxis). Long-term prophylaxis is a term mainly used to describe the long-term (and often indefinite) use of therapeutic anticoagulation in patients with VTE who are at extremely high risk of recurrence if anticoagulation is stopped. Cancer patients with VTE or patients with a second, unprovoked VTE often require long-term prophylaxis or extended-duration VTE treatment. Some data suggest that aspirin might also play a role as secondary prophylaxis once anticoagulation has been stopped after a single idiopathic DVT.[130] Although it does not replace extended-duration anticoagulation when indicated, aspirin is recommended for patients with unprovoked DVT or PE when the decision is made to stop anticoagulation, according to the 2016 update of the guidelines from the American College of Chest Physicians.[131]

In the AMPLIFY-EXT trial, a prophylactic dose of apixaban given as secondary prevention was as effective as a therapeutic dose to prevent VTE recurrence and mortality. This benefit occurred without an increased risk of major bleeding compared with placebo.[132]

Case history

Case history #1

A 70-year-old woman known to have osteoporosis and a previous vertebral fracture presents to the accident and emergency department with a hip fracture after a fall. She has no history of venous thrombosis. On physical examination, her left leg is externally rotated and painful on active and passive motion. The leg is not oedematous and there is no calf tenderness on palpation. Her creatinine clearance is 50 mL/minute and her coagulation parameters are normal. Her surgery is delayed. She is at increased risk of VTE due to trauma and immobility and will be at further risk postoperatively.

Case history #2

A 65-year-old woman with known stage IV ovarian cancer is admitted to hospital with nausea and vomiting of 5 days' duration. On physical examination, her abdomen is distended and tender, and bowel sounds are diminished. An abdominal x-ray shows small bowel dilation, suggesting small bowel obstruction. Laboratory values are consistent with acute renal failure, specifically urea 18 micromol/litre and creatinine 250 micromol/litre. The coagulogram and haemoglobin are normal. She is at increased risk of VTE due to malignancy.

Other presentations

Special considerations when deciding on thromboprophylaxis for patients presenting at risk of VTE include a previous history of heparin-induced thrombocytopenia or thrombocytopenia, or ambulatory patients undergoing chemotherapy associated with a high thrombotic risk. Morbid obesity or weight <50 kg also requires adjustment of the prophylactic dose. Older patients may have impaired renal function and, as a result, creatinine clearance must be calculated to adjust the dose of the anti-thrombotic agents or to avoid agents excreted by the kidney. Certain medications recommended for thromboprophylaxis have not been approved in pregnancy due to teratogenicity or lack of data on safety. Guidelines are available for some of these conditions, but clinical judgement to assess thromboprophylaxis for a given patient is also warranted.

Step-by-step diagnostic approach

Thrombotic risk varies with the reason for admission to hospital and the characteristics of the patient. Physicians should evaluate the risk of VTE in all patients admitted to hospital while also considering bleeding risk and any contraindications to pharmacological VTE prophylaxis. Baseline investigations include renal function and FBC, with coagulation profile if coagulation disorder suspected.

Risk stratification for venous thrombosis

General guidelines address options for prophylaxis according to the type of patient (medical or surgical) and the type of surgery. Thromboprophylaxis must then be tailored to the individual patient in terms of additional VTE risk factors.[4]

Key risk factors include previous VTE (DVT and/or PE), thrombophilia, malignancy, postoperative setting, trauma, indwelling central catheter (upper or lower extremity), and immobility. Other risk factors include chronic medical conditions, admission to intensive care, neurological disease with extremity paresis, increasing age, obesity, oestrogen-containing contraceptive pills and HRT, androgen-depriving therapy, varicose veins, pregnancy and up to 6 weeks postnatal, first-degree relative with a history of VTE, and extended travel. However, these often have conflicting evidence.

Risk stratification for bleeding (patient-related factors, spinal anaesthesia, neurosurgical procedures)

Because pharmacological agents are considered the mainstay of VTE prophylaxis, risk stratification for bleeding must be assessed. Pharmacological agents are contraindicated if the patient presents with active bleeding, severe thrombocytopenia, or a coagulation disorder.[3] Baseline FBC and coagulation parameters (if a coagulation disorder is suspected) help rule out these contraindications. Non-pharmacological agents, including graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices, are recommended in patients at high risk of bleeding.[3] Clinical scores can help assess the risk of bleeding and guide clinical decisions. The IMPROVE bleeding risk score has been prospectively validated and can help make the decision whether to administer a pharmacological thromboprophylaxis.[50] [51]

An assessment of bleeding risk must also consider the presence of neuraxial anaesthesia and analgesia. Unlike therapeutic doses, prophylactic doses of anticoagulation are rarely associated with spinal haematomas,[52] but nonetheless care must be taken to avoid giving anticoagulants close to catheter insertion and removal so that no clinically significant anticoagulant effect is present at the time of the procedure.

Other contraindication to pharmacological agents

A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Even if serum antiplatelet factor 4 (anti-PF4) antibodies are not detectable, avoiding UFH or LMWH for thromboprophylaxis is advisable if alternative agents are available.[53] In these cases, danaparoid can be safely used.[54] Encouraging but still limited data are available on the use of fondaparinux after HIT.[55] [56]

Hypersensitivity to a pharmacological agent is another contraindication requiring the use of an alternative agent.

Baseline tests

Before initiating thromboprophylaxis, all patients should have the following tests performed.

- Renal function: agents such as LMWH and fondaparinux are eliminated through the kidney and must be used with caution in patients with chronic renal failure.[57] [58] Before starting thromboprophylaxis, creatinine should be measured and creatinine clearance subsequently calculated.
- FBC: this will rule out an acute drop in haemoglobin or severe thrombocytopenia, which are contraindications to pharmacological thromboprophylaxis.
- Coagulation profile: this should be ordered if a coagulation disorder is suspected.

- Serum anti-PF4 antibodies: this should be ordered if there is a clinical suspicion of HIT while the patient is receiving UFH or LMWH (>50% drop in platelet counts, arterial or venous thrombosis while the patient is receiving heparin).

Medical patients

Thromboprophylaxis is indicated if the patient is admitted for pulmonary or cardiovascular decompensation; or acute infectious, rheumatic, or inflammatory conditions; or is immobilised due to a medical illness and has one or more additional VTE risk factors.[59] [49]

Recommendations for special medical patients (ICU, cancer [ambulatory], catheter-related)

Almost all critical-care patients should receive thromboprophylaxis.[49] For ambulatory patients with cancer receiving chemotherapy, thromboprophylaxis is generally not indicated.[49] However, there may be a role for thromboprophylaxis in cancer outpatients undergoing chemotherapy who are at high risk for VTE. Trials showed that LMWH prophylaxis can safely reduce VTE rates in various high-risk cancer populations.[60] It should be noted that patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone have a high risk of venous thrombosis. The American Society of Clinical Oncology, the European Society for Medical Oncology, and the International Myeloma Working Group recommend thromboprophylaxis in these patients.[25] [61] [62]

Prophylaxis is not recommended for preventing catheter-related thrombosis.[49] [63]

Surgery

In vascular surgery, thromboprophylaxis is recommended only in patients with additional VTE risk factors or for major procedures (e.g., aortic aneurysm repair, aortofemoral bypass surgery).[3] [4]

In gynaecological, urological, or general surgery, thromboprophylaxis is not indicated if it is a minor procedure (e.g., transurethral procedure) and the patient does not have additional VTE risk factors.[3] The European thromboprophylaxis guidelines suggest graduated compression stockings (GCS) in these low-risk patients.[63] Prophylaxis is recommended after major surgery or if the patient has additional VTE risk factor(s).[3]

In thoracic surgery and CABG, thromboprophylaxis should be routinely used.[3]

Patients undergoing neurosurgery (such as resection of meningioma) are a special population because of the bleeding risk and potential serious consequences of bleeding. Routine mechanical thromboprophylaxis (GCS and intermittent pneumatic compression [IPC] devices) is recommended with the addition of a pharmacological agent in high-risk patients who are at low risk of bleeding.[3] [4] [63]

High-risk groups include trauma patients, orthopaedic surgery patients, and patients with acute spinal cord injury. Major trauma patients should routinely receive pharmacological prophylaxis unless contraindicated. Mechanical prophylaxis may be added in high-risk patients.[3] [63] In high-risk patients undergoing spinal surgery, pharmacological prophylaxis is combined with mechanical prophylaxis if there is no contraindication.

Patients undergoing orthopaedic surgery are an extremely high-risk population.[64] [65] The risk of developing a DVT after a hip or knee replacement is about 40% to 60% without prophylaxis.[47] For hip fracture, total hip replacement, and total knee replacement, routine prophylaxis is warranted. If surgery for

hip fracture is delayed, prophylaxis should be given before the surgery.[47] [63] Thromboprophylaxis for lower-extremity fractures of the tibia, fibula, or ankle is generally not recommended but can be considered if there are additional risk factors for VTE.[47] [63] The incidence of proximal DVT is very low after arthroscopic surgery, regardless of receiving prophylaxis. Thromboprophylaxis after arthroscopic surgery cannot currently be recommended.[66]

Bariatric surgery patients are probably a high-risk population, although fewer data are available. Routine thromboprophylaxis is recommended with weight-adjusted dosing of pharmacological agents.[3]

Risk factors

Strong

previous VTE (DVT and/or PE)

- Previous VTE is a strong independent predictor of new VTE. Patients with previous VTE are 8 times more likely than patients who have never had a VTE to develop a new VTE in a high-risk situation.[15] In a case-control study, previous VTE increased risk of having a second VTE 4.7-fold.[16] Patients with 2 or more episodes of VTE carry an extremely high risk of additional recurrence. Notably, in cases where a definite provocation (such as surgery) of VTE can be identified, the risk of recurrence is lower than it is for patients without an easily identifiable risk factor.

thrombophilia

- Several thrombophilic disorders have been associated with VTE occurrence. Reported risks of VTE with the different thrombophilias vary widely. In acquired thrombophilias, risk of VTE is doubled with anti-cardiolipin antibodies and 5.6-fold greater with lupus anticoagulant.[17] With hereditary thrombophilias, risk is markedly higher in family studies than in case-control studies. For deficiencies of antithrombin, protein C, and protein S, risk is increased 1.7- to 6.5-fold in case-control studies versus 5.0- to 42.8-fold in family studies. For factor V Leiden (heterozygote), risk is increased 5- to 10-fold in case-control studies and 2.5- to 16-fold in family studies. For prothrombin mutation, risk is increased 3-to 4-fold versus patients without the mutation.[17] A combination of thrombophilias or homozygote status confers a greater risk of VTE than that associated with individual thrombophilias or heterozygote status.[17]

malignancy

- The association between malignancy and VTE has been well documented. Compared with non-cancer patients, patients with cancer have a 4- to 7-fold increased risk of VTE.[18] [19]
- Risk varies according to cancer type, cancer stage, and use of chemotherapy.[20] [21] Cancer types most strongly associated with VTE vary from study to study. In a study involving 9 million patients admitted to hospital, cancer types most strongly associated with VTE were uterine, brain, ovarian, and pancreatic.[20] Higher cancer stage at diagnosis is a strong independent risk factor for VTE within the first year following diagnosis.[21] Treatment with chemotherapy further increases the risk of VTE.[22] [23] In a case-control study, chemotherapy in a cancer population was associated with a 6.5-fold greater risk of VTE.[24] Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone have a high risk of venous thrombosis.[25]

postoperative setting

- Surgery is a strong risk factor for VTE. As a general estimate, the risk of VTE following surgery is increased 4- to 22-fold.[17] [24] Certain types of surgery (e.g., orthopaedic) confer a higher risk of VTE than others.

trauma

- One of the strongest risk factors for VTE. In a case-control study, recent trauma was associated with a 13-fold increased risk of VTE.[24]

indwelling central catheter (upper or lower extremity)

- Increases likelihood of DVT and PE by occupying the lumen of the vein and impeding blood flow. Central venous catheter and transvenous pacemaker were associated with a 5.5-fold increased risk of PE or upper extremity DVT in a case-control study.[24] Femoral venous catheters increase the risk of ileofemoral DVT in a similar manner in critically ill patients.[26]

immobility

- Patients admitted to hospital are increasingly disease-burdened, and immobilisation contributes to making them prime candidates to develop VTE. Without prophylaxis, the incidence of symptomatic DVT acquired in hospital is about 10% to 20% in medical patients, 15% to 40% in general surgery patients, and 40% to 60% in major orthopaedic surgery patients.[3] [4]

Weak

myeloproliferative diseases

- Myeloproliferative diseases have been linked to a statistically increased risk of venous thrombosis (especially intra-abdominal clot) in some studies but not in others.[27] [28] [29]

congestive heart failure

- Congestive heart failure is generally considered to be an independent risk factor for VTE, but 2 studies did not confirm a significant relationship in multivariate analyses.[17] [19] [24]

chronic obstructive pulmonary disease

- Chronic obstructive pulmonary disease is not a strong independent risk factor for VTE because no significant relationship was found in various studies.[19] [29]

inflammatory bowel disease

- Inflammatory bowel disease tripled the risk of VTE in patients with Crohn's disease and ulcerative colitis,[30] but this was not confirmed in a second study.[29]

neurological disease with extremity paresis

- Often results in immobilisation and is thus an important risk factor for VTE. In a case-control study, neurological disease with extremity paresis was associated with a tripled risk of VTE.[24]

increasing age

- Independent risk factor for VTE, with a 1.7- to 1.9-fold increase per decade.[18] [31]

obesity

- The relationship between VTE and obesity is controversial. No association was found in the Heart and Estrogen/Progestin Replacement Study (HERS), but a 2.9-fold increase in PE with a BMI >29 kg/m^2 was documented in the Nurses' Health Study.[19] [32]

oestrogen-containing contraceptive pills, HRT, and androgen deprivation therapy

- Hormone therapy has been documented to be a risk factor for VTE in numerous studies. With respect to age-matched non-users, the risk of VTE with contraceptive pill use is estimated to increase 2- to 4-fold.[33] The risk is highest in the first year of contraceptive pill use.[34] Postmenopausal HRT also doubles or triples the VTE risk.[19] [35] The absolute risk of VTE is much higher with HRT than with contraceptive pill use, because the baseline risk of VTE is higher in postmenopausal than in younger women.[36] In one study, patients receiving androgen deprivation therapy for prostate cancer had an 84% increase in their VTE risk.[37]

hx of varicose veins

- Inconsistent link to VTE in various studies. In one study, varicose veins increased the risk of DVT by a factor of 2.6.[38] In another study, the risk of VTE associated with varicose veins varied with age. It was increased 4-fold in 45-year-old patients and doubled in 60-year-old patients; it was not increased in 75-year-old patients.[29] Finally, in the Framingham study, varicose veins were not an independent predictor of PE at autopsy.[39]

pregnancy/postnatal

- In Western countries, PE is the leading cause of maternal death during pregnancy.[40] Pregnancy was an independent risk factor for VTE in various studies.[36] [41] In the Sirius study, the increase in VTE associated with pregnancy was 11-fold.[42]

extended travel

- There seems to be a mild risk of VTE associated with prolonged travel.[43] In a univariate analysis, extended travel was 2.4 times more frequent in outpatients presenting with a DVT.[42] Long flights (>8-10 hours) are more strongly associated with VTE.[44] However, not all studies found a significant relationship between extended travel and development of VTE.[45]

lower leg immobility

- Patients with lower leg trauma and lower leg immobility with a plaster cast or brace are at increased risk of developing DVT. One Cochrane review of 6 RCTs showed a significantly lower rate of VTE in patients with lower leg immobility with daily prophylaxis compared with those without prophylaxis or with placebo.[46] However, because the primary outcome of these studies included asymptomatic DVT confirmed by screening venography or ultrasonography, routine thromboprophylaxis in patients with lower leg immobility is not recommended.[47]

first-degree relative with a history of VTE

- In a Swedish study, the risk of recurrent hospitalisation for idiopathic VTE was 1.20 (95% confidence interval [CI] 1.10–1.32) for people whose parents had a history of VTE, and 1.30 (95% CI 1.14–1.49) for those with affected siblings. The risk of recurrent VTE hospitalisation in people with 2 affected parents was 1.92 (95% CI 1.44–2.58).[48]

admission to intensive care

- According to the 2012 version of the guidelines from the American College of Chest Physicians, the risk of symptomatic DVT is around 58 per 1000 patients and the risk of PE is around 42 per 1000 patients. These risks vary with pre-existing medical illnesses, the nature of the acute illness as well as the presence of surgery, catheters, and anaesthesia.[49]

History & examination factors

Key diagnostic factors

previous VTE, thrombophilia, malignancy, postoperative setting, trauma, and indwelling central catheter (common)

- These are key strong risk factors for VTE.

chronic medical conditions, paresis, increasing age, obesity, oestrogen-containing contraceptive pills and HRT, varicose veins, pregnancy and up to 6 week postnatal, first-degree relative with a history of VTE, extended travel, and admission to intensive care (common)

- These are additional, weaker risk factors for VTE.

Diagnostic tests

1st test to order

Test	Result
FBC • Should be ordered before initiating prophylaxis. Acute drop in haemoglobin or severe thrombocytopenia is a contraindication to pharmacological thromboprophylaxis.	**acute drop in haemoglobin suggests active bleeding; severe thrombocytopenia increases risk of bleeding**
serum creatinine • Should be ordered before initiating prophylaxis. Severe renal insufficiency requires dose adjustment or use of an agent not excreted through the kidney.	**increased creatinine indicates severe renal insufficiency (creatinine clearance <30 mL/minute)**
INR • Should be ordered if a coagulation disorder is suspected. In this case, pharmacological prophylaxis could be contraindicated.	**variable; increased in some underlying coagulation disorders**
PTT • Should be ordered if a coagulation disorder is suspected. In this case, pharmacological prophylaxis could be contraindicated.	**variable; increased in some underlying coagulation disorders**

Other tests to consider

Test	Result
serum antiplatelet factor 4 antibodies • Should be ordered if clinical suspicion of heparin-induced thrombocytopenia while the patient is receiving unfractionated heparin or low molecular weight heparin (>50% drop in platelet counts; arterial or venous thrombosis while the patient is receiving heparin).	**antiplatelet factor 4 antibodies may be present**

Step-by-step treatment approach

Evaluation of the VTE risk, as well as consideration of the bleeding risk and any contraindications to pharmacological VTE prophylaxis, should be undertaken in all patients prior to the administration of VTE prophylaxis. VTE prophylaxis entails pharmacological and non-pharmacological measures to diminish the risk of DVT and PE.

Pharmacological thromboprophylaxis has been shown to be effective and safe in both medical and surgical patient populations.[59] Thromboprophylaxis with unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux in surgical settings diminishes the rate of symptomatic and asymptomatic VTE by at least 60% compared with placebo.[67] [68]

Knowledge translation of clinical guidelines into clinical practice is a significant challenge. Overall, only 40% to 50% of medical patients admitted to hospital receive adequate thromboprophylaxis. Adherence to guidelines is higher in surgical patients but remains limited.[69] [70] Developing thromboprophylaxis guidelines in each hospital to guide clinicians is strongly recommended. Moreover, methods such as computer-based decision systems and pre-printed orders, whereby physicians are confronted with decision-making for each individual patient, have been shown to be most effective in optimising adherence to thromboprophylaxis guidelines.[71] [72] Periodic audits by pharmacists or other health professionals reinforce the consistent use of VTE prophylaxis.[73] The direct oral anticoagulants, including direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors (e.g., rivaroxaban and apixaban), that are being licensed for thromboprophylaxis in orthopaedic patients in Europe, Canada, and the US might improve adherence in the future if thromboprophylaxis studies show safety and efficacy in other hospital patient populations.[74] [75] [76] [77] [78] [79] [80] [81] Dissemination of information through networks such as the Canadian-based Safer Health Care Now network[82] also contributes to global awareness of the importance of VTE in the hospital setting.[83] [84]

Types of prophylaxis measure (pharmacological and non-pharmacological)

Pharmacological agents should be considered the mainstay of VTE prophylaxis, together with early ambulation. Three pharmacological agents have been approved for some time: unfractionated heparin (UFH), low molecular weight heparin (LMWH), and the selective anti-Xa inhibitor fondaparinux. Warfarin is a reasonable alternative but it requires frequent monitoring. The use of aspirin alone for thromboprophylaxis is controversial.[47] Evidence for combined prophylaxis with 28 days of aspirin after total hip replacement surgery has been shown to be non-inferior to, and as safe as, dalteparin for prevention of VTE in patients who initially received 10 days of dalteparin.[85]

Other oral agents, such as direct thrombin inhibitors (dabigatran) and anti-Xa inhibitors (rivaroxaban, apixaban) have now been approved in Canada and Europe for hip and knee replacement surgery, but not for hip fracture surgery. The FDA in the US has also approved rivaroxaban and apixaban for this indication. Unlike warfarin, oral anti-Xa inhibitors and direct thrombin inhibitors require no monitoring when used as prophylactic agents. Rivaroxaban, dabigatran, and apixaban are recommended by the American College of Chest Physicians (ACCP) guidelines and the National Institute for Care and Excellent (NICE) UK guidelines for reducing the risk of venous thromboembolism after elective hip and knee replacement.[47] [76] [86] [87] Dabigatran must not be used in patients with mechanical prosthetic valves, either in a prophylactic or therapeutic setting.[88] Rivaroxaban and apixaban have also been studied for thromboprophylaxis in medical patients. The MAGELLAN trial, a phase III trial comparing rivaroxaban versus enoxaparin in medical patients, showed that rivaroxaban was non-inferior to enoxaparin with

regard to the primary efficacy endpoint, but that bleeding was significantly increased.[89] Bleeding was also an issue in the ADOPT trial comparing apixaban with enoxaparin in medical patients.[90]

Other characteristics of the direct oral anticoagulants include a twice daily dose for apixaban versus a once daily dose with dabigatran and rivaroxaban. Dabigatran is not recommended in patients with a CrCl <30 mL/minute, especially if it is co-administered with a P-glycoprotein inhibitor. Rivaroxaban is also not recommended in patients with a CrCl <30 mL/minute. Apixaban should be used with caution in patients with a CrCl <30 mL/minute. All direct oral anticoagulants are started postoperatively as indicated in the individual product monographs. LWMH can be started preoperatively or postoperatively, but the authors recommend that LMWH be started after surgery because of concerns about the risk of bleeding into the joint.

Non-pharmacological agents include graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices. IPC devices significantly decrease the rate of DVT versus placebo, but they are not as effective as pharmacological agents; on a background of pharmacological prophylaxis they do provide some benefit.[3] [91] [92] [93] Therefore, these devices should generally be used without concomitant pharmacological thromboprophylaxis only if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis. IPC devices can also be added to pharmacological agents in selected high-risk patients, such as those with cancer undergoing major surgery. Significant limitations to the use of compression stockings is the fact that early mobilisation is cumbersome with the device and that adherence is an issue. However, mobile compressive devices show interesting results since they can be comfortably worn while the patient is walking and the time of use is recorded by the device.[94] Data on graduated compression stockings in medical and stroke patients prompted new recommendations not to use these devices since there was no benefit and significant skin damage.[95] [96] Although evidence from one meta-analysis found fewer pulmonary embolisms with inferior vena cava filter use compared with no inferior vena cava filter use in trauma patients, there was no difference in incidence of DVT or mortality.[97] Inferior vena cava filters are currently not recommended for thromboprophylaxis.

Medical patients

Thromboprophylaxis is generally recommended for most hospitalised medical patients, except for patients who are at low risk for VTE. The use of risk assessment models has been suggested to estimate baseline risks for patients at low and high risk for VTE. One of the risk assessment models suggested by the American College of Chest Physicians is the Padua Prediction Score.[49] The assessment of all hospitalised medical patients for risk of VTE is important so that appropriate thromboprophylaxis can be provided.

If the patient is admitted for pulmonary or cardiovascular decompensation, or acute infectious, rheumatic, or inflammatory conditions, and is immobilised due to a medical illness, with one or more additional VTE risk factors, thromboprophylaxis with UFH, LMWH, or fondaparinux is recommended until either full mobility is restored or the patient is discharged from hospital.[49] Rivaroxaban has been found non-inferior to enoxaparin for thromboprophylaxis in medical patients; however, bleeding was significantly increased with this agent.[89] In a study that compared apixaban with enoxaparin in medically ill patients,[90] the extended course of apixaban (30 days) was not superior to a shorter course of enoxaparin and was associated with significantly more bleeding. Extended use of thromboprophylaxis in medically ill patients beyond the period of hospitalisation or patient immobilisation is not currently recommended.[49] [98] Certain subgroups of medical patients, such as acutely ill patients with recently

reduced mobility, might benefit from extended thromboprophylaxis, but further studies are needed.[99] [100]

Medical patients (ICU, cancer [ambulatory])

Most critical care patients should receive thromboprophylaxis and UFH or LMWH is generally recommended. No agent has been clearly shown superior in terms of efficacy or bleeding.[101] In the PROTECT trial, among 3675 critical care patients randomly assigned to prophylactic dose of dalteparin versus UFH, dalteparin was not superior to UFH in preventing thrombosis.[101] There are no data on fondaparinux or the direct oral anticoagulants in this population.

Hospitalised cancer patients if immobilised should receive thromboprophylaxis with LMWH, UFH, or fondaparinux.[49] The American Society for Clinical Oncology and the European Society of Medical Oncology recommend prophylactic LMWH, UFH, or fondaparinux in hospitalised cancer patients.[102] [62]

There is no clear consensus on thromboprophylaxis of ambulatory cancer patients receiving chemotherapy, and in general, widespread thromboprophylaxis is not recommended.[49] [62] [103] [104] A predictive model using the Khorana score on a computer platform has been validated in a prospective trial, and can help to assess the risk of VTE in cancer patients.[105] It should be noted that patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at a high risk for venous thrombosis. Accordingly, the American Society of Clinical Oncology recommends prophylactic LMWH or low-dose aspirin for multiple myeloma patients receiving thalidomide or lenalidomide.[62]

The International Myeloma Working Group and the National Comprehensive Cancer Network recommend aspirin in low-risk myeloma patients with 1 VTE risk factor; and recommend LMWH or therapeutic warfarin in high-risk patients with 2 or more risk factors.[25] [104] The European Society of Medical Oncology does not recommend prophylaxis for advanced cancer patients receiving chemotherapy, but recommends considering LMWH, aspirin, or adjusted-dose warfarin (INR ~1.5) in myeloma patients receiving thalidomide plus dexamethasone or thalidomide plus chemotherapy.[103] However, a systematic review found that aspirin may not be an adequate thromboprophylaxis for patients with multiple myeloma receiving lenalidomide plus high-dose dexamethasone.[106]

Finally, the 2012 American College of Chest Physicians guidelines suggest prophylactic dose LMWH or low-dose UFH in outpatients with solid tumours, who have additional risk factors for VTE and are at low risk of bleeding. Additional risk factors include previous VTE, immobilisation, hormonal therapy, angiogenesis inhibitors, and thalidomide or lenalidomide therapy.[49] Evidence for this suggestion is weak and further trials are needed to clarify this question.

Thromboprophylaxis is not recommended for preventing catheter-related thrombosis.[49] [62] [103] [104]

Surgical patients

The American College of Chest Physicians suggests 2 risk assessment models that take into consideration patient- and procedure-specific risk factors to estimate baseline risk factors of surgical patients.[3] The first risk assessment model is the Rogers score which stratifies patients from very low (<7 points), to low (7-10 points), to moderate risk (>10 points) for VTE. Because the Rogers score is somewhat cumbersome to use and has not been externally validated, the American College of Chest Physicians also suggests a relatively easy-to-use model called the Caprini score, which has been validated in a sample of general, vascular, and urological surgery patients. The Caprini score categorises

patients as being at very low (0 points), low (1-2 points), moderate (2-3 points), or high risk (≥5 points) for VTE.[3]

In general surgery, gynaecological, urological, gastrointestinal, and vascular surgery, pharmacological thromboprophylaxis is not indicated if the patient is at low risk for VTE (Caprini score 1-2; or Rogers score 7-10), but mechanical prophylaxis (preferably with IPC) is recommended.[3] In the European thromboprophylaxis guidelines, GCS are usually recommended in low-risk patients.[63] However, prophylaxis with UFH or LMWH plus mechanical prophylaxis is recommended for high-risk patients (e.g., major surgery or the patient has additional VTE risk factor(s)).[3] Fondaparinux can be used in a postoperative setting for gastrointestinal surgery.[4] For high-risk surgical cancer patients, thromboprophylaxis with UFH or LMWH with extended prophylaxis up to 4 weeks after surgery can be considered, as well as adding IPC devices or GCS.[3] [4] [63]

In thoracic surgery and cardiac surgery, thromboprophylaxis should be routinely used. Mechanical prophylaxis (stockings or intermittent pneumatic compression) is recommended for patients undergoing thoracic surgery, with the addition of LMWH and UFH in patients at low risk of major bleeding.[4] Most patients undergoing cardiac surgery (including CABG) are considered at moderate risk for VTE and at high risk for major bleeding complications. The 2012 American College of Chest Physicians guidelines recommend mechanical prophylaxis for patients with an uncomplicated postoperative course and suggest adding UFH or LMWH in patients with a prolonged hospital course with 1 or more non-haemorrhagic surgical complications.[3]

Patients undergoing neurosurgery (such as resection of meningioma) are a special population because of the bleeding risk and potential serious consequences of bleeding. In neurosurgery, routine thromboprophylaxis with IPC devices is recommended.[3] [4] [63] In patients at low risk of major bleeding, UFH or LMWH should be added to IPC devices if not contraindicated.[3] [4] [63]

High-risk groups include trauma patients, orthopaedic surgery patients, and patients with acute spinal cord injury. Trauma patients should routinely receive prophylaxis with UFH, LMWH, and/or mechanical methods, preferably IPC, until discharge unless contraindicated.[3] [63] In surgery for acute spinal cord injury, prophylaxis with UFH or LMWH is started after surgery and continued for 3 months or until the patient is fully ambulatory.[3] IPC devices are used if pharmacological prophylaxis is contraindicated or preferably in association with UFH or LMWH in these two high-risk groups.[3] [4] [63]

Patients undergoing orthopaedic surgery are an extremely high-risk population.[64] [65] For total hip replacement and total knee replacement, LMWH, fondaparinux, apixaban, rivaroxaban, dabigatran, UFH, warfarin, aspirin, and/or an intermittent pneumatic compression device can be used as prophylaxis, with preference for LMWH.[47] [63] [93]The NICE UK guidelines suggest a combination of pharmacological and mechanical thromboprophylaxis.[4] Low-quality evidence suggests aspirin for prevention of VTE after total knee replacement and total hip replacement surgery.[63] Based on 4 randomised trials,[107] [108] [109] [110] dabigatran etexilate has been approved in Canada and Europe for this indication, but not in the US. The RECORD (REgulation of Coagulation in ORthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) series of phase III studies of rivaroxaban showed a significant decrease in total VTE without an increase in bleeding compared with enoxaparin for total knee replacement and total hip replacement surgeries.[74] [111] [112] [113] Rivaroxaban has been approved in Canada, the US, and in Europe for thromboprophylaxis after total hip or total knee replacement. Apixaban has also been approved in Europe, the US, and Canada for thromboprophylaxis following hip and knee arthroplasty based on the ADVANCE-2 and ADVANCE-3 trials.[114] [115] Rivaroxaban, dabigatran, and apixaban are recommended by the American College of Chest Physicians (ACCP) guidelines and

the NICE UK guidelines for reducing the risk of venous thromboembolism after elective hip and knee replacement, but not for hip fracture surgery.[47] [76] [86] [87]

For hip fracture surgery, LMWH, fondaparinux, low-dose UFH, warfarin, aspirin, or an intermittent pneumatic compression device are recommended for prophylaxis, with preference for LMWH.[47] [63] The NICE UK guidelines suggest a combination of pharmacological and mechanical thromboprophylaxis.[4] If surgery for hip fracture is delayed, LMWH or UFH should be given at least 12 hours before the surgery.[47] [63] The minimum duration of postoperative thromboprophylaxis is 10 to 14 days. Extended prophylaxis up to 35 days from the day of surgery is recommended for patients undergoing major orthopaedic surgery, as well as the addition of IPC during the hospital stay.[47] [63] [116]

Thromboprophylaxis for lower-extremity fractures of the tibia, fibula, or ankle is generally not recommended but can be considered if there are additional risk factors for VTE.[47] [63] The incidence of proximal DVT is very low after arthroscopic surgery, regardless of receiving prophylaxis. Thromboprophylaxis after arthroscopic surgery cannot currently be recommended.[66]

Bariatric surgery patients are probably also a high-risk population, although data are more limited. Thromboprophylaxis with LMWH, fondaparinux, or UFH is recommended, with the possible addition of mechanical devices.[3] Higher doses of LMWH and UFH should be used in obese patients.

Special situations (renal failure, obesity, pregnancy, HIT)

LMWH, fondaparinux, rivaroxaban, apixaban, and dabigatran are eliminated through the kidney and must be used with caution in patients with chronic renal failure.[57] [58] Few data are available on the use of LMWH with reduced creatinine clearance (<30 mL/minute), because these patients have been excluded from randomised controlled trials. Three options are suggested: use UFH, reduce the dose of LMWH according to the manufacturer's instructions, or measure anti-Xa levels.[3] Because no level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH, we do not recommend routine anti-Xa level monitoring. The dose of enoxaparin can be reduced according to the manufacturer's instructions. Preliminary data show that bio-accumulation of anti-Xa activity may vary with different LMWH molecules.[117] For example, among patients with a creatinine clearance <30 mL/minute, 2 studies showed no bio-accumulation of anti-Xa activity with prophylactic doses of dalteparin.[118] [119] Further studies will need to clarify whether a particular LMWH is safer in patients with chronic renal failure. Fondaparinux is contraindicated in patients with severe renal insufficiency (creatinine clearance <30 mL/minute). Dabigatran is not recommended in patients with a CrCl <30 mL/minute, especially if it is co-administered with a P-glycoprotein inhibitor. Rivaroxaban is also not recommended in patients with a CrCl <30 mL/minute. Apixaban should be used with caution in patients with a CrCl <30 mL/minute.

In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3]

For pregnant women requiring thromboprophylaxis, UFH and LMWH are safe because they do not cross the placenta. The 2012 American College of Chest Physicians guidelines recommend the prophylactic use of LMWH over UFH for pregnant patients.[120] Insufficient data are available on fondaparinux, rivaroxaban, or dabigatran to approve their use in pregnancy.

A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to UFH or LMWH. Even if serum antiplatelet factor 4 antibodies are not detectable, avoiding UFH or LMWH for

thromboprophylaxis is advisable if alternative agents are available.[53] Consultation with a thrombosis specialist is warranted to determine the best treatment option, as these agents have a long half-life and no antidote. Danaparoid has been safely used in these cases and is available in some European countries, Australia, and Canada, but is not available in the US.[54] Moreover, it must be used with caution when haemostasis is inadequate because it has a prolonged half-life (24 hours) and no antidote. There are very few data to support the use of prophylactic subcutaneous lepirudin after HIT. Recombinant hirudin is used in some European countries. Desirudin (recombinant hirudin analogue) was approved in 2003 for prevention of VTE after elective hip surgery, but only recently marketed in the US. Disadvantages of desirudin are the lack of antidote and the potential development of anti-hirudin antibodies. Encouraging, but still limited, data are available on the use of fondaparinux after HIT, and it can be considered for thromboprophylaxis after HIT for patients in the US.[56] Similarly to danaparoid, fondaparinux must be used with caution when haemostasis is inadequate because it has a prolonged half-life (21 hours) and no antidote. The production of lepirudin has been discontinued, so this agent is no longer available.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Presumptive (summary)

Patient group	Tx line	Treatment
all at-risk patients	**1st**	**early mobilisation**

Acute (summary)

Patient group	Tx line	Treatment
trauma patients	**1st**	**low molecular weight heparin or unfractionated heparin**
	adjunct	**graduated compression stockings or intermittent pneumatic compression devices**
	2nd	**graduated compression stockings or intermittent pneumatic compression devices alone**
major orthopaedic surgery	**1st**	**low molecular weight heparin or unfractionated heparin or fondaparinux or warfarin or rivaroxaban or dabigatran or apixaban or aspirin**
major orthopaedic surgery	**adjunct**	**graduated compression stockings or intermittent pneumatic compression devices**

Acute (summary)

major orthopaedic surgery	2nd	graduated compression stockings or intermittent pneumatic compression devices alone
minor orthopaedic surgery without additional VTE risk factors	1st	graduated compression stockings
minor orthopaedic surgery with additional risk factors for VTE	1st	low molecular weight heparin
minor orthopaedic surgery with additional risk factors for VTE	adjunct	graduated compression stockings or intermittent pneumatic compression devices
bariatric surgery	1st	low molecular weight heparin or unfractionated heparin or fondaparinux
bariatric surgery	adjunct	graduated compression stockings or intermittent pneumatic compression devices
bariatric surgery	2nd	graduated compression stockings or intermittent pneumatic compression devices alone
vascular surgery	1st	low molecular weight heparin or unfractionated heparin
vascular surgery	adjunct	graduated compression stockings or intermittent pneumatic compression devices
vascular surgery	2nd	graduated compression stockings and intermittent pneumatic compression devices alone
minor gynaecological, urological, or general surgery, including laparoscopic surgery, without additional VTE risk factors	1st	graduated compression stockings
major gynaecological, urological, or general surgery or with additional VTE risk factors	1st	low molecular weight heparin or unfractionated heparin
major gynaecological, urological, or general surgery or with additional VTE risk factors	adjunct	extended prophylaxis + graduated compression stockings and/or intermittent pneumatic compression devices
major gynaecological, urological, or general	2nd	graduated compression stockings or intermittent pneumatic compression devices alone

Acute (summary)

surgery or with additional VTE risk factors		
thoracic surgery	1st	low molecular weight heparin or unfractionated heparin
thoracic surgery	adjunct	graduated compression stockings or intermittent pneumatic compression devices
thoracic surgery	2nd	graduated compression stockings or intermittent pneumatic compression devices alone
cardiac surgery	1st	intermittent pneumatic compression devices
cardiac surgery	adjunct	low molecular weight heparin or unfractionated heparin
neurosurgery	1st	intermittent pneumatic compression devices
neurosurgery	adjunct	low molecular weight heparin or unfractionated heparin
elective spinal surgery	1st	intermittent pneumatic compression devices
elective spinal surgery	adjunct	low molecular weight heparin or unfractionated heparin
with pulmonary or cardiovascular decompensation, or acute infectious, rheumatic, or inflammatory conditions, or immobilised with one or more additional VTE risk factors	1st	low molecular weight heparin or unfractionated heparin or fondaparinux
ICU patient	1st	low molecular weight heparin or unfractionated heparin
ICU patient	adjunct	graduated compression stockings or intermittent pneumatic compression devices
ICU patient	2nd	graduated compression stockings or intermittent pneumatic compression devices alone
cancer patients receiving thalidomide or lenalidomide	1st	low molecular weight heparin or low-dose warfarin or aspirin
cancer patients receiving thalidomide or lenalidomide	adjunct	graduated compression stockings or intermittent pneumatic compression devices

Treatment options

Presumptive

Patient group	Tx line	Treatment
all at-risk patients	**1st**	**early mobilisation** » Early mobilisation should be encouraged to diminish the likelihood of developing a VTE.

Acute

Patient group	Tx line	Treatment
trauma patients	**1st**	**low molecular weight heparin or unfractionated heparin** » Major trauma patients should receive thromboprophylaxis with low molecular weight heparin (LMWH) or low-dose unfractionated heparin (UFH) until discharge unless contraindicated.[3] [63] » In surgery for acute spinal cord injury, prophylaxis with LMWH is started after surgery if haemostasis is adequate and continued until the patient is fully ambulatory. » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best medication to use. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Final choice of agent to be used should be based on evidence-based data as well as local preferences.

Acute

Patient group	Tx line	Treatment
		» If spinal/epidural anaesthesia is considered, thromboprophylaxis must be discussed with the anaesthetist. » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin
	adjunct	**graduated compression stockings or intermittent pneumatic compression devices** » For trauma patients at high risk for VTE (including patients with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), adding mechanical prophylaxis, such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices, to pharmacological prophylaxis is recommended when not contraindicated by lower-extremity injury.[3] [4] [121] [122] IPC devices are preferred in patients with acute spinal cord injury and in trauma patients.[3] [63] Although evidence from one meta-analysis found fewer pulmonary embolisms with inferior vena cava filter use compared with no inferior vena cava filter use in trauma patients, there was no difference in incidence of DVT or mortality.[97] Inferior vena cava filters are currently not recommended for thromboprophylaxis.
	2nd	**graduated compression stockings or intermittent pneumatic compression devices alone** » Non-pharmacological agents such as graduated compression stockings (GCS) and

Acute

Patient group	Tx line	Treatment
		intermittent pneumatic compression (IPC) devices are not as effective as pharmacological agents.[3] They should be used alone only if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis. IPC devices are preferred in patients with acute spinal cord injury and in trauma patients.[3] [63] Although evidence from one meta-analysis found fewer pulmonary embolisms with inferior vena cava filter use compared with no inferior vena cava filter use in trauma patients, there was no difference in the incidence of DVT or mortality.[97] Inferior vena cava filters are currently not recommended for thromboprophylaxis.
major orthopaedic surgery	**1st**	**low molecular weight heparin or unfractionated heparin or fondaparinux or warfarin or rivaroxaban or dabigatran or apixaban or aspirin** » Patients undergoing orthopaedic surgery are an extremely high-risk population.[64] [65] For total hip replacement and total knee replacement, low molecular weight heparin (LMWH) is the preferred agent for thromboprophylaxis, although fondaparinux, low-dose unfractionated heparin (UFH), or warfarin can also be used as prophylaxis.[47] [63] Warfarin should be started (5-10 mg orally daily) the night before surgery or on the night of the surgery. In addition, rivaroxaban, apixaban, and dabigatran have been approved by Canada and Europe for hip and knee replacement surgery, but not for hip fracture surgery.[74] [75] [76] [77] [78] [79] [80] [81] The Food and Drug Administration (FDA) in the US has approved rivaroxaban and apixaban for thromboprophylaxis in hip and knee replacement surgery, but not for hip fracture surgery. Rivaroxaban, dabigatran, and apixaban are recommended by the American College of Chest Physicians (ACCP) guidelines and the National Institute for Care and Excellent (NICE) UK guidelines for reducing the risk of venous thromboembolism after elective hip and knee replacement, but not for hip fracture surgery.[47] [76] [86] [87] Dabigatran must not be used in patients with mechanical prosthetic valves, either in a prophylactic or therapeutic setting.[88] » There is low-quality evidence to suggest aspirin for prevention of VTE after total knee

Acute

Patient group	Tx line	Treatment
		replacement, total hip replacement, and hip fracture surgery.[63] Evidence for combined prophylaxis with 28 days of aspirin after total hip replacement surgery has been shown to be non-inferior to, and as safe as, dalteparin for prevention of VTE in patients who initially received 10 days of dalteparin.[85] » Minimum duration of thromboprophylaxis is 10-14 days. Extended prophylaxis up to 35 days is recommended for total hip replacement, hip fracture surgery, and total knee replacement. For fondaparinux, a duration of up to 32 days for hip replacement and fracture is recommended. Treatment with enoxaparin should be for 28-35 days. Extended prophylaxis should also be considered after knee surgery, but the recommendation is much weaker for total knee replacement.[47] [48] [63] » If surgery for hip fracture is delayed, LMWH or unfractionated heparin (UFH) should be given at least 12 hours before surgery.[47] [63] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option, as these agents have a long half-life and no antidote. Danaparoid has been safely used in these patients, but data on orthopaedic patients are limited.[54] It is available in some European countries, Australia, and Canada, but is not available in the US. Desirudin (recombinant hirudin analogue) is for use in patients with a history of HIT only. It was approved in 2003 for prevention of VTE after elective hip surgery, but only recently marketed in the US. Encouraging but still limited data are available on the use of fondaparinux after HIT, and it can be considered for thromboprophylaxis after HIT for patients in the US.[56] » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3]

Acute

Patient group	Tx line	Treatment

Fondaparinux is contraindicated in patients with severe renal insufficiency (creatinine clearance <30 mL/minute). Dabigatran is not recommended in patients with a CrCl <30 mL/minute, especially if it is co-administered with a P-glycoprotein inhibitor. Rivaroxaban is also not recommended in patients with a CrCl <30 mL/minute. Apixaban should be used with caution in patients with a CrCl <30 mL/minute.

» If surgery is under spinal/epidural anaesthesia, postoperative thromboprophylaxis must be discussed with the anaesthetist.

» Consult specialist or local protocols for guidance on dose.

Primary options

» enoxaparin

OR

Primary options

» tinzaparin

OR

Primary options

» dalteparin

OR

Primary options

» heparin

OR

Primary options

» fondaparinux

OR

Primary options

» warfarin

OR

Primary options

» rivaroxaban

OR

Primary options

Acute

Patient group	Tx line	Treatment
		» dabigatran **OR** **Primary options** » apixaban **OR** **Secondary options** » aspirin **OR** **Secondary options** » desirudin **OR** **Secondary options** » danaparoid sodium
major orthopaedic surgery	**adjunct**	**graduated compression stockings or intermittent pneumatic compression devices** » Adding non-pharmacological agents such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices to pharmacological prophylaxis is recommended when there is no contraindication.[122] Although select reports show some benefit using venous foot pumps in prevention of VTE, the evidence is of low quality.[93] » Inferior vena cava filters are not recommended for thromboprophylaxis.
major orthopaedic surgery	**2nd**	**graduated compression stockings or intermittent pneumatic compression devices alone** » Non-pharmacological agents such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices are not as effective as pharmacological agents.[47] Although select reports show some benefit using venous foot pumps in prevention of VTE, the evidence is of low quality.[91] [93] Therefore, GCS or IPC devices should be used alone only if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis.

Acute

Patient group	Tx line	Treatment
		» Inferior vena cava filters are not recommended for thromboprophylaxis.
minor orthopaedic surgery without additional VTE risk factors	**1st**	**graduated compression stockings** » Thromboprophylaxis is generally not indicated for minor orthopaedic surgery if the patient does not have additional VTE risk factors.[47] [123] » In the European thromboprophylaxis guidelines, graduated compression stockings (GCS) are usually recommended in these patients.[63] Early ambulation should be encouraged.
minor orthopaedic surgery with additional risk factors for VTE	**1st**	**low molecular weight heparin** » Thromboprophylaxis is generally not indicated for minor orthopaedic surgeries, but can be considered if there are additional risk factors for VTE (previous VTE, thrombophilia, malignancy, trauma, indwelling central catheter [upper or lower extremity], immobility, chronic medical conditions, neurological disease with extremity paresis, increasing age, obesity, oestrogen-containing contraceptive pills and HRT, history of varicose veins, pregnancy, extended travel). » If surgery is under spinal/epidural anaesthesia, postoperative thromboprophylaxis must be discussed with the anaesthetist. » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin
minor orthopaedic surgery with additional risk factors for VTE	**adjunct**	**graduated compression stockings or intermittent pneumatic compression devices** » Non-pharmacological agents such as graduated compression stockings (GCS) and intermittent pneumatic compression

TREATMENT

Acute

Patient group	Tx line	Treatment
		(IPC) devices can be added to treatment with pharmacological agents. » Inferior vena cava filters are not recommended for thromboprophylaxis.
bariatric surgery	**1st**	**low molecular weight heparin or unfractionated heparin or fondaparinux** » Probably a high-risk population, although fewer data are available. Thromboprophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) or fondaparinux is recommended with the possible addition of mechanical devices until the patient is mobile.[3] [4] Thromboprophylaxis should continue until the risk of VTE has diminished and the patient is mobile. Fondaparinux should not be started preoperatively. » In obese patients, weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] [124] » A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to LMWH or UFH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Fondaparinux is contraindicated in patients with severe renal insufficiency (creatinine clearance <30 mL/minute). » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options**

Acute

Patient group	Tx line	Treatment
		» fondaparinux **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin
bariatric surgery	**adjunct**	**graduated compression stockings or intermittent pneumatic compression devices** » Non-pharmacological agents such as graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) devices can be added to treatment with pharmacological agents in selected high-risk patients. » Inferior vena cava filters are not recommended for thromboprophylaxis.
bariatric surgery	**2nd**	**graduated compression stockings or intermittent pneumatic compression devices alone** » Non-pharmacological agents such as graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) devices are not as effective as pharmacological agents.[3] Therefore, GCS or IPC devices should be used alone only if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis. » Inferior vena cava filters are not recommended for thromboprophylaxis.
vascular surgery	**1st**	**low molecular weight heparin or unfractionated heparin** » Thromboprophylaxis with low molecular weight heparin (LMWH) and unfractionated heparin (UFH) is recommended until discharge only in patients with additional VTE risk factors, after major procedures (e.g., repair of aortic aneurysm), and at low risk of major bleeding.[3] [4] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable

Acute

Patient group	Tx line	Treatment
		to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin
vascular surgery	**adjunct**	**graduated compression stockings or intermittent pneumatic compression devices** » Non-pharmacological agents such as graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) devices can be added to treatment with pharmacological agents in selected high-risk patients if there is no peripheral arterial disease. » Inferior vena cava filters are not recommended for thromboprophylaxis.

Acute

Patient group	Tx line	Treatment
vascular surgery	**2nd**	**graduated compression stockings and intermittent pneumatic compression devices alone** » Non-pharmacological agents such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices are not as effective as pharmacological agents.[3] Therefore, GCS or IPC devices should be used alone only if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis. » Inferior vena cava filters are not recommended for thromboprophylaxis.
minor gynaecological, urological, or general surgery, including laparoscopic surgery, without additional VTE risk factors	**1st**	**graduated compression stockings** » Thromboprophylaxis is not indicated if it is a minor procedure (e.g., transurethral procedure) and the patient does not have additional VTE risk factors.[3] In the European thromboprophylaxis guidelines, graduated compression stockings (GCS) are usually recommended in low-risk patients.[63] Early ambulation should be encouraged.
major gynaecological, urological, or general surgery or with additional VTE risk factors	**1st**	**low molecular weight heparin or unfractionated heparin** » Prophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is recommended in patients at low risk of major bleeding if it is major surgery or the patient has additional VTE risk factor(s).[3] [4] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3]

Acute

Patient group	Tx line	Treatment
		» If spinal/epidural anaesthesia is considered, thromboprophylaxis must be discussed with the anaesthetist. » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin
major gynaecological, urological, or general surgery or with additional VTE risk factors	**adjunct**	**extended prophylaxis + graduated compression stockings and/or intermittent pneumatic compression devices** » For high-risk gynaecological or general surgery patients (e.g., previous history of VTE or major surgery in a cancer patient), extended prophylaxis up to 28 days can be considered, as well as the addition of intermittent pneumatic compression (IPC) devices or graduated compression stockings (GCS).[3] [4] [63] [122]
major gynaecological, urological, or general surgery or with additional VTE risk factors	**2nd**	**graduated compression stockings or intermittent pneumatic compression devices alone** » Non-pharmacological agents such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices are not as effective as pharmacological agents.[3] Therefore, GCS or IPC devices should be used alone only if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis » Inferior vena cava filters are not recommended for thromboprophylaxis.

Acute

Patient group	Tx line	Treatment
thoracic surgery	1st	**low molecular weight heparin or unfractionated heparin** » Thromboprophylaxis should be routinely used. Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) are routinely recommended if patients are at low risk of major bleeding.[3] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] The dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin
thoracic surgery	adjunct	**graduated compression stockings or intermittent pneumatic compression devices**

Acute

Patient group	Tx line	Treatment
		» Non-pharmacological agents such as graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) devices can be added to treatment with pharmacological agents in selected high-risk patients.[122] » Inferior vena cava filters are not recommended for thromboprophylaxis.
thoracic surgery	2nd	**graduated compression stockings or intermittent pneumatic compression devices alone** » Non-pharmacological agents such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices are not as effective as pharmacological agents.[3] Therefore, GCS or IPC devices should be used alone if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis. » Inferior vena cava filters are not recommended for thromboprophylaxis.
cardiac surgery	1st	**intermittent pneumatic compression devices** » For patients undergoing CABG with a high risk of bleeding, the American College of Chest Physicians (ACCP) recommends the optimal use of mechanical thromboprophylaxis. » Intermittent pneumatic compression devices are preferred over graduated compression stockings. » Inferior vena cava filters are not recommended for thromboprophylaxis.
cardiac surgery	adjunct	**low molecular weight heparin or unfractionated heparin** » Thromboprophylaxis should be routinely used. Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are recommended.[3] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH or UFH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3]

Acute

Patient group	Tx line	Treatment
		» A past history of HIT is an important contraindication to LMWH or UFH. However, UFH is sometimes used for the surgical procedure once the anti-platelet factor 4 antibodies have disappeared. Exposure to heparin is then minimised by choosing an alternative agent. Consultation with a thrombosis specialist may be warranted to determine the best option, as these agents have a long half-life and no antidote. Encouraging but still limited data are available on the use of danaparoid or fondaparinux after HIT, and they can be considered for thromboprophylaxis after HIT for patients in the US.[56] » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin
■ **neurosurgery**	**1st**	**intermittent pneumatic compression devices** » Patients undergoing neurosurgery (such as resection of meningioma) are a special population because of the bleeding risk and potential serious consequences of bleeding. Routine thromboprophylaxis with mechanical measures such as intermittent pneumatic compression (IPC) devices is recommended.[3] [4] [63] Unfractionated heparin or low molecular

Acute

Patient group	Tx line	Treatment
		weight heparin should be added to IPC devices if not contraindicated and patients are at a low risk of major bleeding.[3] [63]
neurosurgery	**adjunct**	**low molecular weight heparin or unfractionated heparin** » Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) should be added to intermittent pneumatic compression devices if not contraindicated.[3] [63] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin

Acute

Patient group	Tx line	Treatment
elective spinal surgery	1st	**intermittent pneumatic compression devices** » Routine thromboprophylaxis with intermittent pneumatic compression (IPC) devices is recommended.[3] [4] [63]
elective spinal surgery	adjunct	**low molecular weight heparin or unfractionated heparin** » If additional VTE risk factors are present, a combination of pharmacological methods (low molecular weight heparin [LMWH] or unfractionated heparin [UFH]) with intermittent pneumatic compression (IPC) devices can be used once adequate haemostasis is established and the risk of bleeding decreases.[3] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin

Acute

Patient group	Tx line	Treatment
		OR
		Primary options
		» heparin
with pulmonary or cardiovascular decompensation, or acute infectious, rheumatic, or inflammatory conditions, or immobilised with one or more additional VTE risk factors	**1st**	**low molecular weight heparin or unfractionated heparin or fondaparinux** » If the patient is 1) admitted for pulmonary or cardiovascular decompensation, or acute infectious, rheumatic, or inflammatory conditions, or is immobilised due to a medical illness and 2) has one or more additional VTE risk factors, thromboprophylaxis with unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux is recommended until either full mobility is restored or the patient is discharged from hospital.[49] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » Data from clinical trials of apixaban and rivaroxaban as thromboprophylaxis in medical patients found increased bleeding risk with these agents, and their use is not recommended.[89] [90] » A past history of heparin-induced thrombocytopenia (HIT) is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] Fondaparinux is contraindicated in patients with severe renal insufficiency (creatinine clearance <30 mL/minute). » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin

Acute

Patient group	Tx line	Treatment
		OR **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin **OR** **Primary options** » fondaparinux
ICU patient	**1st**	**low molecular weight heparin or unfractionated heparin** » Critical-care patients should receive thromboprophylaxis. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are both accepted.[49] » In obese patients (BMI >30 kg/m^2), weight-based prophylactic LMWH dosing is preferable to fixed dosing.[3] Dose can be adjusted empirically for patients <50 kg who are at risk of bleeding, but guidelines do not address this issue.[3] » A past history of heparin-induced thrombocytopenia is an important contraindication to LMWH. Consultation with a thrombosis specialist is warranted to determine the best treatment option. » In patients with renal insufficiency, unfractionated heparin or LMWH (e.g., enoxaparin, dose-adjusted according to the manufacturer's instructions) may be used. No level of anti-Xa has been shown to be effective and safe for prophylactic doses of LMWH.[3] » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin

Acute

Patient group	Tx line	Treatment
		OR **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » heparin
ICU patient	**adjunct**	**graduated compression stockings or intermittent pneumatic compression devices** » Non-pharmacological agents such as graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) devices can be added to treatment with pharmacological agents in selected higher-risk patients. » Inferior vena cava filters are not recommended for thromboprophylaxis.
ICU patient	**2nd**	**graduated compression stockings or intermittent pneumatic compression devices alone** » Non-pharmacological agents such as graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) devices are not as effective as pharmacological agents.[49] [120] Therefore, GCS or IPC devices should be used alone if pharmacological agents are contraindicated. Once the contraindication has resolved, the patient should receive pharmacological prophylaxis. » Inferior vena cava filters are not recommended for thromboprophylaxis.
cancer patients receiving thalidomide or lenalidomide	**1st**	**low molecular weight heparin or low-dose warfarin or aspirin** » For ambulatory patients with cancer receiving chemotherapy, thromboprophylaxis is generally not indicated.[49] [62] [103] [104] Patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone have a high risk of venous thrombosis. The American Society

Acute

Patient group	Tx line	Treatment
		of Clinical Oncology recommends prophylactic low molecular weight heparin (LMWH) or low-dose aspirin.[62] » The International Myeloma Working Group and the National Comprehensive Cancer Network recommend aspirin if there is one VTE risk factor, and prophylactic LMWH or therapeutic warfarin if there are 2 or more risk factors.[25] [104] The 2012 American College of Chest Physician guidelines suggest thromboprophylaxis in cancer outpatients with solid tumours who are at low risk of bleeding with 1 or more additional VTE risk factors, which includes thalidomide or lenalidomide.[49] » Consult specialist or local protocols for guidance on dose. **Primary options** » enoxaparin **OR** **Primary options** » tinzaparin **OR** **Primary options** » dalteparin **OR** **Primary options** » warfarin **OR** **Primary options** » aspirin
cancer patients receiving thalidomide or lenalidomide	**adjunct**	**graduated compression stockings or intermittent pneumatic compression devices** » Non-pharmacological agents such as graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) devices can be added to treatment with pharmacological agents in selected high-risk patients.

Acute

Patient group	Tx line	Treatment
		» Inferior vena cava filters are not recommended for thromboprophylaxis.

Emerging

Betrixaban

An oral direct factor Xa inhibitor. A randomised, double-blind phase III trial involving patients hospitalised for an acute illness and at risk for VTE found no significant difference between extended-duration betrixaban versus standard-duration enoxaparin for preventing VTE.[125] Major bleeding events were similar for both drugs. The US Food and Drug Administration has approved betrixaban for VTE prophylaxis in adults hospitalised for an acute illness who are at risk for VTE.

Edoxaban

An oral direct factor Xa inhibitor. A randomised, double-blind phase III trial involving patients with acute VTE has found edoxaban to be non-inferior to warfarin for preventing recurrent VTE.[126] Major bleeding events were similar for both drugs. Edoxaban is approved in Europe for preventing recurrent VTE, but it is not approved in the US for this indication.

Recommendations

Monitoring

It is important to monitor daily for signs and symptoms of VTE. Non-invasive testing (venous duplex, V/Q scan, or CT angiography) is recommended if VTE is suspected. Routine screening with these tests is not recommended in asymptomatic patients.

Patients should also be monitored for bleeding, especially in the postoperative setting. For example, bleeding can occur at the site of surgery, from a gastric or duodenal ulcer, or at low molecular weight heparin (LMWH) or unfractionated heparin (UFH) injection sites. If bleeding is suspected, haemoglobin and coagulation parameters should be ordered and anticoagulation discontinued.

To detect heparin-induced thrombocytopenia (HIT), measuring platelet count is recommended at least every other day for patients at highest risk for HIT, primarily post-surgical patients receiving prophylactic UFH. For surgical patients receiving either prophylactic LMWH or UFH catheter flushes, as well as for medical patients receiving prophylactic UFH, platelet count monitoring at least every 2 to 3 days is recommended for 4 to 14 days following the onset of prophylaxis. Routine platelet count monitoring is not recommended for medical patients receiving prophylactic LMWH (low risk).[3] However, any patient receiving UFH or LMWH prophylaxis who develops either a venous or arterial thrombotic event, or a necrotic reaction at an injection site, must have a haemogram to measure platelets and assess for HIT.

Patient instructions

Patients must be educated as to signs and symptoms suggesting VTE (e.g., swelling, pain, redness, or venous distension in a limb, as well as pleuritic chest pain or dyspnoea) because 75% of postoperative VTE occurs following discharge from hospital. Patients should be instructed to consult their physician immediately if they experience any of these symptoms or if they experience necrotic reactions at an injection site, because this may suggest HIT. Finally, patients should seek immediate medical attention for symptoms suggesting a severe allergic reaction, such as breathing difficulty, wheezing, and swelling of the face, lips, tongue, or throat.

Early mobilisation should be encouraged to diminish the likelihood of developing a VTE. If long-term prophylaxis is given, pre-arranging for patients to practise injections or for community-based organisations to be involved in giving the injections is recommended.

Complications

Complications	Timeframe	Likelihood
DVT	**short term**	**medium**
VTE prophylaxis diminishes the risk of developing a VTE, but it does not nullify it. Therefore, the treating physicians and nurses should routinely look for signs and symptoms of DVT when patients are admitted to hospital. If DVT is suspected, proper diagnostic testing must be performed rapidly to rule out this potentially deadly complication. Early mobilisation facilitated by attending staff on the wards is strongly encouraged to diminish the likelihood of developing a clot. Moreover, thromboprophylaxis should not be interrupted unless there is a valid reason (e.g., active bleeding). Mechanical thromboprophylaxis should then be implemented.		

FOLLOW UP

Complications	Timeframe	Likelihood
PE	**short term**	**medium**

Due to high mortality in the early stages of PE,[127] aggressive treatment is necessary in the case of high-risk patients (modified Wells' score >4, systolic BP <90 mmHg). Hypoxaemia with systolic BP <90 mmHg suggests massive PE, which has a high mortality.

O2/ALS protocol, haemodynamic support (including judicious use of inotropics), and anticoagulation with low molecular weight or unfractionated heparin should be instituted without delay in all patients who present with these high-risk features.

Deciding whether to initiate thrombolysis or anticoagulation should be made on a case-by-case basis according to clinical presentation, risk of PE, and pre-existing morbidity. This tends to vary according to local expertise and centre provision.

Inferior vena cava filter placement and surgical embolectomy may be appropriate when anticoagulation and/or thrombolytics are contraindicated. Risk/benefit decisions need to be made on an individual basis according to local provision and clinical presentation.

Following the acute phase, long-term anticoagulation with warfarin should be tailored to the underlying condition (e.g., thrombophilia) and risk factors.[128]

anticoagulant-related bleeding	**short term**	**low**

The risk of anticoagulant bleeding varies according to type of anticoagulant (mode of administration, half-life, and reversibility) and patient risk factors (medical/surgical, coagulopathy). Prophylactic doses obviously cause less bleeding than therapeutic doses. In addition, the definition of major and minor bleeding is not standard across studies, and the reported incidence of bleeding in the literature varies.

Risk factors for bleeding (e.g., active peptic ulcer disease, liver disease, thrombocytopenia, post-surgical haemostasis, neuraxial anaesthesia) must be thoroughly assessed before any decision to prescribe prophylactic anticoagulants. Daily clinical assessments of bleeding as well as monitoring of haemoglobin help to identify any source of bleeding early.

Managing anticoagulation-associated bleeding depends on the location and severity of bleeding. It usually necessitates promptly removing the anticoagulant, giving an antidote if available (for unfractionated heparin [UFH], low molecular weight heparin [LMWH], and warfarin), and giving support treatment using transfusions. For example, Kcentra, a prothrombin complex concentrate that contains 4 vitamin K-dependent factors, including factor II, factor VII, factor IX, and factor X, as well as protein C and S, is approved for the reversal of vitamin-K antagonist mediated bleeding. Kcentra is marketed as Beriplex or Confidex in more than 25 countries.

No antidote is currently available for the direct oral anticoagulants rivaroxaban and apixaban. Prothrombin complex concentrates can be administered following the manufacturer's recommendations, but no large published studies support the efficacy of this approach. Idarucizumab, a monoclonal antibody binding dabigatran, was found to be effective at normalising coagulation tests in the REVERSE-AD trial.[129] It is now approved by the US Food and Drug Administration (FDA) and in Canada for reversal of dabigatran's anticoagulation effects in emergency situations. Although data are limited, dabigatran (but not rivaroxaban or apixaban) seems to be removed by dialysis.

heparin-induced thrombocytopenia	**short term**	**low**

Complications	Timeframe	Likelihood
Heparin-induced thrombocytopenia (HIT) is a rare but serious complication in patients who are receiving or who have recently received heparin. It is usually manifested by a 50% or greater platelet count drop 5 to 14 days after starting a course of heparin. It is more commonly associated with UFH than with LMWH. HIT can therefore be prevented by using LMWH rather than UFH as a prophylactic agent. Thrombosis is an important complication of HIT. To detect HIT, measuring platelet count is recommended at least every other day for the highest-risk patients (post-surgical patients receiving prophylactic UFH). For surgical patients receiving prophylactic LMWH or UFH catheter flushes, as well as for medical patients receiving prophylactic UFH, measuring platelet counts at least every 2 to 3 days is recommended for 4 to 14 days. No routine platelet count is recommended for medical patients receiving prophylactic LMWH (low risk).[3] However, any patient developing thrombosis or necrotic reaction at the injection site while receiving UFH or LMWH should have an FBC to measure platelets. If HIT is suspected, referral to a haematologist or thrombosis specialist is recommended.		
allergic reaction to anticoagulant agents	**short term**	**low**
Reactions can include severe, life-threatening symptoms such as breathing difficulties, wheezing, and angio-oedema with swelling of the face, lips, tongue, or throat. These reactions require immediate medical assistance. Less severe reactions include an allergic rash or injection site reactions. For all these reactions, discontinuing the offending agent is recommended and a physician should be consulted.		

Prognosis

Most patients will not develop VTE while receiving thromboprophylaxis. However, some patients will break through if thromboprophylaxis is not given adequately or if they are particularly prothrombotic. The treating physicians and nurses should routinely look for signs and symptoms of DVT or PE when patients are admitted to hospital. If VTE is suspected, proper diagnostic testing must be performed rapidly to rule out this potentially deadly complication.

Patients receiving pharmacological thromboprophylaxis

Thromboprophylaxis with a pharmacological agent can also be complicated by bleeding or, less frequently, allergic reactions and heparin-induced thrombocytopenia.

Treatment guidelines

Europe

Thrombosis and embolism during pregnancy and the puerperium, reducing the risk

Published by: Royal College of Obstetricians and Gynaecologists **Last published:** 2015

Summary: Provides evidence-based advice on the prevention of VTE during pregnancy and birth, and following delivery.

Prevention and management of venous thromboembolism

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2015

Summary: Provides evidence-based guidance on the assessment of risk for VTE, thromboprophylaxis in surgical and medical patients, risk assessment and thromboprophylaxis in pregnancy and the puerperium, and travel-related thrombosis. It outlines the diagnosis, and initial and further management of VTE. It also describes the monitoring of anticoagulant effect and details the adverse effects of VTE prophylaxis and treatment.

Venous thromboembolism: reducing the risk for patients in hospital

Published by: National Institute for Health and Care Excellence **Last published:** 2015

Summary: UK perspective on thromboprophylaxis. The following recommendations were identified as priorities for implementation: assessing the risk of VTE and major bleeding, reducing risk of VTE, and providing patient information and discharge planning.

Antithrombotics: indications and management

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2013

Summary: Provides evidence-based guidance on the use of anticoagulants as prophylaxis and treatment.

Apixaban for the prevention of venous thromboembolism after total hip or knee replacement in adults

Published by: National Institute for Health and Care Excellence **Last published:** 2012

Summary: Provides guidance and recommendations for the use of apixaban to reduce the risk of VTE in adults having orthopaedic surgery (hip or knee replacement).

Management of venous thromboembolism (VTE) in cancer patients: ESMO clinical practice guidelines

Published by: European Society of Medical Oncology **Last published:** 2011

Summary: Provides evidence-based recommendations for the prevention and treatment of VTE in patients with cancer.

Europe

Rivaroxaban for the prevention of venous thromboembolism after total hip or total knee replacement in adults

Published by: National Institute for Health and Care Excellence **Last published:** 2009

Summary: Provides guidance regarding use of rivaroxaban to reduce the risk of VTE in adults having orthopaedic surgery (hip or knee replacement).

2008 SOR guidelines for the prevention and treatment of thrombosis associated with central venous catheters in patients with cancer: report from the working group

Published by: Working group of the SOR; French National Federation of Cancer Centres **Last published:** 2009

Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults

Published by: National Institute for Health and Care Excellence **Last published:** 2008

Summary: Provides guidance and recommendations for the use of dabigatran to reduce the risk of VTE in adults having orthopaedic surgery (hip or knee replacement).

International

Prevention and treatment of venous thromboembolism: international consensus statement

Published by: Cardiovascular Disease Educational and Research Trust; European Venous Forum; North American Thrombosis Forum; International Union of Angiology; Union Internationale du Phlebologie **Last published:** 2013

Summary: Details various methods available to prevent and manage venous thromboembolism.

Prevention and treatment of venous thromboembolism: international consensus statement (guidelines according to scientific evidence)

Published by: Cardiovascular Disease Educational and Research Trust; Cyprus Cardiovascular Disease Educational and Research Trust; European Venous Forum; International Surgical Thrombosis Forum; International Union of Angiology; Union Internationale de Phlebologie **Last published:** 2006

Summary: Guidelines with authors predominantly from Europe. Provides recommendations on prevention and treatment of deep vein thrombosis and pulmonary embolism, management of recurrent idiopathic venous thromboembolism, VTE in cancer patients, and management of heparin-induced thrombocytopenia.

North America

Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report

Published by: American College of Chest Physicians **Last published:** 2016

Summary: This guideline provides recommendations on antithrombotic therapy for VTE disease.

NCCN clinical practice guidelines in oncology: cancer-associated venous thromboembolic disease

Published by: National Comprehensive Cancer Network **Last published:** 2016

Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update

Published by: American Society of Clinical Oncology **Last published:** 2015

Summary: Provides recommendations on prophylaxis and treatment of VTE in patients with cancer. Prophylaxis in the outpatient, inpatient, and perioperative settings is considered, as is treatment and use of anticoagulation as a cancer-directed therapy.

Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Provides evidence-based recommendations on the treatment and prevention of heparin-induced thrombocytopenia.

Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Provides evidence-based recommendations on the optimal prophylaxis to reduce postoperative VTE.

Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Provides evidence-based recommendations on VTE prevention in hospitalised medical patients, outpatients with cancer, the chronically immobilised, long-distance travellers, and those with asymptomatic thrombophilia.

North America

Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines

Published by: American College of Chest Physicians **Last published:** 2012

Summary: Provides evidence-based recommendations on the optimal prophylaxis to reduce postoperative pulmonary embolism and DVT following major orthopaedic surgery.

Guidelines for deep venous thrombosis prophylaxis during laparoscopic surgery

Published by: Society of American Gastrointestinal and Endoscopic Surgeons **Last published:** 2006

Summary: Provides guidance on risk stratification and recommendations for VTE prophylaxis in patients undergoing laparoscopic surgery.

Practice parameters for the prevention of venous thrombosis

Published by: American Society of Colon and Rectal Surgeons **Last published:** 2006

Summary: Provides risk-based recommendations for VTE prophylaxis in patients undergoing colorectal surgery.

Africa

Venous thromboembolism: prophylactic and therapeutic practice guideline

Published by: Southern African Society of Thrombosis and Haemostasis **Last published:** 2013

Summary: Provides a concise, practical guideline for VTE prophylaxis and treatment in medical and surgical patients.

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DISCLOSURES: VT declares that she has received an investigator-initiated grant from Sanofi-Aventis. She has also received consultancy fees from Bristol-Myers Squibb, Leo Pharma, Pfizer, and Sanofi-Aventis. VT is an author of a reference cited in this monograph.

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