Can J Anesth/J Can Anesth (2015) 62:194–202
DOI 10.1007/s12630-014-0262-2

REVIEW ARTICLE/BRIEF REVIEW

Prevention of venous thromboembolism in the Enhanced Recovery After Surgery (ERAS) setting: an evidence-based review

Prévention des thromboembolies veineuses dans le cadre de la Récupération rapide après la chirurgie (RRAC): une synthèse basée sur les données probantes

Benjamin R. Bell, MD · Pascal E. Bastien, MD · James D. Douketis, MD · on behalf of Thrombosis Canada

Received: 16 May 2014 / Accepted: 24 October 2014 / Published online: 13 November 2014

Abstract

Purpose *To review the evidence surrounding appropriate prophylaxis for venous thromboembolism (VTE) in patients undergoing surgery.*

Principal findings *Appropriate prophylactic strategies for surgical patients have been defined in major society guidelines. We review the evidence behind these guidelines in a case-based format, including patients with a high risk of bleeding, history of heparin-induced thrombocytopenia, obesity, and cancer. Selecting the most suitable means for VTE prophylaxis includes evaluating patient, anesthetic, and surgical factors. Nevertheless, pharmacologic VTE prophylaxis will be appropriate for the vast majority of inpatients undergoing surgery.*

Conclusions *Venous thromboembolism is a serious but preventable complication of hospitalization, especially among surgical patients. Historically, it has accounted for a high burden of postoperative morbidity and mortality. In the Enhanced Recovery After Surgery era, our aim should be no less ambitious than the eradication of postoperative VTE.*

Résumé

Objectif *Étudier les données probantes entourant la prophylaxie adéquate pour les épisodes thromboemboliques veineux (TEV) chez les patients subissant une chirurgie.*

Constatations principales *Les stratégies de prophylacxie adéquate pour les patients chirurgicaux ont été définies dans les principales lignes directrices des sociétés prédominantes. Nous examinons les données probantes qui sous-tendent ces lignes directrices sous forme d'études de cas, en incluant des patients avec un risque hémorragique élevé, des antécédents de thrombocytopénie induite par l'héparine, d'obésité et de cancer. Le choix des moyens les plus adaptés pour la prophylaxie des épisodes de TEV inclut l'évaluation des facteurs liés au patient, à l'anesthésie et à la chirurgie. Néanmoins, une prophylaxie pharmacologique de la TEV sera appropriée pour la grande majorité des patients hospitalisés subissant une chirurgie.*

Conclusions *Les épisodes thromboemboliques veineux sont une complication grave mais évitable de l'hospitalisation, en particulier chez les patients chirurgicaux. Ils ont historiquement représenté une large part de la morbidité et de la mortalité postopératoire. À l'ère de la Récupération rapide après la chirurgie, notre objectif ne devrait pas avoir d'autre ambition que l'éradication de la TEV postopératoire.*

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common vascular disease after coronary artery disease and stroke, affecting 1-2 per 1,000

B. R. Bell, MD (✉) · P. E. Bastien, MD
Division of General Internal Medicine, North York General Hospital, 4001 Leslie Street, Willowdale, ON M2K 1E1, Canada
e-mail: ben.bell@utoronto.ca

B. R. Bell, MD · P. E. Bastien, MD
Department of Medicine, University of Toronto, Toronto, ON, Canada

J. D. Douketis, MD
Clinical Thromboembolism and General Internal Medicine Services, St. Joseph's Hospital, Hamilton, ON, Canada

J. D. Douketis, MD
Department of Medicine, McMaster University, Hamilton, ON, Canada

adults in the general population annually.[1] Virchow's triad of endothelial injury, venous stasis, and hypercoagulability, the classically described risk factors for VTE, are all present in the perioperative setting, thereby contributing to the high incidence of postoperative VTE. Thus, in patients having orthopedic surgery without thromboprophylaxis, rates of symptomatic DVT and PE are approximately 3% and 1.5% at 35 days, respectively.[2]

Venous thromboembolism warrants significant attention due to its sizeable morbidity and mortality. The all-cause case fatality rate for PE is estimated to be as high as 9%.[3] Clot extension, embolism, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension are additional complications of VTE that justify the implementation of tailored preventative strategies.

Non-pharmacologic prophylaxis strategies, comprising elastic compression stockings and intermittent pneumatic compression (IPC) devices, are used in patients at high risk of bleeding in the perioperative setting. Pharmacologic strategies, which comprise unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, direct-acting oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban), and acetylsalicylic acid can be used as standalone methods or in conjunction with the non-pharmacologic strategies for VTE prophylaxis in patients undergoing surgery. In all patients, early mobilization is emphasized.[2,4,5]

The appropriate utilization of perioperative VTE prophylaxis is a major pillar in the Enhanced Recovery After Surgery (ERAS) movement for two reasons: First, early mobilization, an important component of mitigating the risk for postoperative VTE, has led to reduced rates of VTE after hip and knee replacement surgery.[6] Second, the appropriate administration (dose and timing) of perioperative anticoagulant prophylaxis is important to mitigate the risk for both VTE and wound-site bleeding and to facilitate the administration of surgical anesthesia and postoperative analgesia, which by themselves can facilitate patient recovery.[7] Against this background, the objectives of this article are (a) to review, through case-based scenarios, the evidence surrounding VTE prophylaxis; (b) to discuss a recently recommended and validated stratification model for postoperative VTE; and (c) to provide state-of-the-art guidance for perioperative prophylaxis. We address special populations, including cancer surgery, bariatric patients, those with a history of heparin-induced thrombocytopenia (HIT) or heparin allergy, and neuraxial anesthesia.

Table 1 The Caprini score

Caprini Score			
1 point (each item)	2 points (each item)	3 points (each item)	5 points (each item)
Age 41-60	Age 61-74	Age ≥ 75	Joint arthroplasty
Minor surgery planned	Major surgery (>45 min)	History of VTE	Hip, pelvis, or leg fracture (<1 month)
Varicose veins	Arthroscopic surgery	Family history of VTE	Stroke (<1 month)
History of inflammatory bowel disease	Laparoscopic surgery (> 45 min)	Factor V Leiden	Trauma (<1 month)
Current swollen legs	Current or previous malignancy	Prothrombin 20210A	Spinal cord injury (<1 month)
BMI > 25	Patient confined to bed (>72 h)	Elevated serum homocysteine	
Acute myocardial infarction	Immobilizing plaster cast (<1 month)	Positive lupus anticoagulant	
Heart failure (<1 month)	Central venous access	Heparin-induced thrombocytopenia	
Sepsis (<1 month)		Other congenital or acquired thrombophilia	
Serious lung disease (<1 month)			
Abnormal pulmonary function			
Medical patient currently at bed rest			
On hormone therapy			
Pregnancy/postpartum (<1 month)			
Unexplained or recurrent miscarriage			

Very low risk (<0.5%): 0 points; Low risk (1.5%): 1-2 points; Moderate risk (3%): 3-4 points; High risk (6%): score > 4 points. BMI = body mass index; VTE = venous thromboembolism

Table 2 Recommended thromboprophylaxis options based on risk for VTE and bleeding

Patient Group	Prophylaxis options	Duration
General and abdominal-pelvic surgery at very low risk for VTE (< 0.5%, Caprini score: 0)	No specific pharmacologic or mechanical prophylaxis other than early ambulation	n/a
General and abdominal-pelvic surgery at very low risk for VTE (1.5%, Caprini score: 1-2)	IPC/ECS (preferably IPC)	n/a
General and abdominal-pelvic surgery at moderate risk for VTE (3%, Caprini score: 3-4) *and* not at high risk for bleeding	LMWH or UFH IPC/ECS (preferably IPC)	7-10 days or until discharge
General and abdominal-pelvic surgery at moderate risk for VTE (3%, Caprini score: 3-4) *and* high risk for bleeding	IPC/ECS (preferably IPC)	7-10 days or until discharge
General and abdominal-pelvic surgery at high risk for VTE (6%, Caprini score: > 4) *and* not at high risk for bleeding	LMWH or UFH IPC/ECS (preferably IPC) should be added to pharmacologic prophylaxis	7-10 days or until discharge
General and abdominal-pelvic surgery at high risk for VTE (6%, Caprini score: >4) *and* high risk for bleeding	IPC/ECS (preferably IPC) Initiate LMWH or UFH when bleeding risk diminishes	7-10 days or until discharge
General and abdominal-pelvic *cancer* surgery at high risk for VTE (6%, Caprini score: > 4) *and* not at high risk for bleeding	LMWH	30 days
Cardiac surgery	IPC/ECS (preferably IPC) Add LMWH or UFH if hospitalization is prolonged.	7-10 days or until discharge
Thoracic surgery at moderate risk for VTE (3%, Caprini score: 3-4) *and* not at high risk for bleeding	LMWH or UFH or IPC/ES (preferably IPC)	7-10 days or until discharge
Thoracic surgery at high risk for VTE (6%, Caprini score: > 4) *and* not at high risk for bleeding	LMWH or UFH IPC/ECS (preferably IPC) should be added to pharmacologic prophylaxis	7-10 days or until discharge
Thoracic surgery at moderate or high risk for VTE *and* high risk for bleeding	IPC/ECS (preferably IPC) Initiate LMWH or UFH when bleeding risk diminishes	7-10 days or until discharge
Craniotomy	IPC/ECS (preferably IPC)	7-10 days or until discharge
Craniotomy at very high risk for VTE (e.g., cancer resection)	IPC/ECS (preferably IPC) Initiate LMWH or UFH when bleeding risk diminishes	7-10 days or until discharge
Spinal surgery	IPC/ECS (preferably IPC)	7-10 days or until discharge
Spinal surgery at very high risk for VTE (e.g. cancer resection)	IPC/ECS (preferably IPC) Initiate LMWH or UFH when bleeding risk diminishes	7-10 days or until discharge
Trauma surgery	LMWH or UFH or IPC/ECS (preferably IPC)	7-10 days or until discharge
Trauma surgery at very high risk for VTE (e.g., spinal cord injury, traumatic brain injury)	LMWH or UFH IPC/ECS (preferably IPC) should be added to pharmacologic prophylaxis (if not contraindicated by lower extremity trauma)	7-10 days or until discharge
Trauma surgery at high risk for bleeding	IPC/ECS (preferably IPC) Initiate LMWH or UFH when bleeding risk diminishes	7-10 days or until discharge

LMWH, e.g., dalteparin 5,000 IU *sc daily*, enoxaparin 40 mg *sc daily*, enoxaparin 30 mg *sc* bid, tinzaparin 3,500 IU *sc daily*; UFH 5,000 units *sc* bid. VTE = venous thromboembolism; IPC/ECS = intermittent pneumatic compression/elastic compression stocking; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin

Table 3 Suggested thromboprophylaxis in orthopedic surgery patients

Patient Group	Prophylaxis Options		Duration
Hip or knee arthroplasty	Rivaroxaban	10 mg *po* daily	14-35 days
	Apixaban	2.5 mg *po* twice daily	
	Enoxaparin	30 mg *sc* twice daily or 40 mg *sc* daily	
	Dalteparin	5,000 U *sc* daily	
	Tinzaparin	4,500 U *sc* daily or 75 $U \cdot kg^{-1}$ daily	
Hip fracture	Enoxaparin	Pre-op: 30 mg *sc* daily	14-35 days
		Post-op: 40 mg *sc* daily	
	Dalteparin	Pre-op: 2,500 U *sc* daily	
		Post-op: 5,000 U *sc* daily	
	Tinzaparin	Pre-op: 3,500 U *sc* daily	
		Post-op: 4,500 U *sc* daily	
Major orthopedic trauma	Low-molecular-weight heparin (LMWH) (enoxaparin 30 mg *sc* twice daily, dalteparin 5,000 U *sc* once daily, or tinzaparin 4,500 U *sc* once daily) when hemostasis is evident Mechanical method if high risk for bleeding with switch to LMWH when bleeding risk decreases		Until discharge (including rehabilitation)
Spine surgery:	a. Mobilization alone		Until discharge (including rehabilitation)
a. Uncomplicated	b. LMWH once daily starting the day after surgery		
b. Complicated (cancer, leg weakness, prior VTE, combined anterior/posterior approach)			
Isolated below-knee fracture	None, if outpatient or overnight hospital stay, LMWH once daily if inpatient		Until discharge (including rehabilitation)
Knee arthroscopy:	a. None		5-30 days
a. Low risk	b. LMWH once daily		
b. Higher risk (major knee reconstruction, prior VTE)			
Lower extremity amputation	LMWH once daily		Until discharge (including rehabilitation)
Other: bedrest, incision & drainage, etc.	LMWH once daily		Until discharge

LMWH = low-molecular-weight heparin; VTE = venous thromboembolism

Case 1

A 76-yr-old male with type-2 diabetes and prior DVT five years ago following a transatlantic flight is scheduled for an elective transurethral resection of the prostate under general anesthesia for benign prostatic hypertrophy refractory to medical therapy.

When considering risk of perioperative VTE, patient- and procedure-specific factors should be assessed. In major orthopedic surgery, which includes hip fracture surgery, total hip arthroplasty, and total knee arthroplasty, the procedure-specific risk outweighs patient factors, and pharmacologic prophylaxis is indicated for at least seven to ten days and, more typically, for 30-35 days (see case 2).

In non-orthopedic surgery, patient factors are also considered when assessing risk of VTE. Risk-stratification for VTE seeks to classify patients into risk categories (very low $< 0.5\%$, low $\sim 1.5\%$, moderate $\sim 3\%$, and high $\sim 6\%$) using a validated model such as the Caprini score[8] shown in Table 1. This score includes age, type and duration of surgery, obesity, history of VTE or thrombophilia, presence of a central venous catheter, and malignancy. Risk of bleeding, analyzed in terms of frequency and severity, depends largely on the type of surgery; patients at highest risk include those undergoing plastic surgery with free flap, cardiac surgery, craniotomy, spinal surgery, and traumatic brain and spine surgery.[5]

Although practically all hospitalized surgical patients (i.e., not having day surgery) are at sufficient risk by the Caprini score to warrant thromboprophylaxis, the modality may vary. Suggested thromboprophylaxis regimens are summarized in Table 2. Decisions regarding pharmacological prophylaxis in surgical patients should be made after consideration of risk factors for both VTE and bleeding. We suggest that every institution should have a written policy for VTE prophylaxis in surgical patients. In general, patients at a moderate or high risk of VTE with at most a moderate risk of bleeding should receive pharmacologic prophylaxis. When such patients have a high risk of bleeding, they should receive mechanical prophylaxis with IPC. The risk of bleeding should be reassessed daily, and pharmacologic prophylaxis should be instituted when the risk is acceptably low.[4]

The patient discussed in the case is at high risk for perioperative VTE (Caprini score = 6) given his age and prior DVT. The surgery is associated with a short-term increased risk of bleeding. Overall, he should receive pharmacologic VTE prophylaxis for at least seven to ten days, initiated when there is adequate hemostasis (e.g., postoperative hematuria begins to resolve), but it should be extended if there is inadequate mobilization given the history of immobility-associated DVT.

Case 2

An 89-yr-old female with osteoporosis had a fall at her retirement home resulting in a displaced subtrochanteric fracture necessitating hip fracture surgery with spinal anesthesia. The surgery is delayed by 24 hr due to other emergent cases.

Although advances in surgical technique coupled with early mobilization have reduced rates of postoperative VTE, patients having major orthopedic surgery remain at high risk for VTE. In the era that preceded widespread use of thromboprophylaxis, the incidences of DVT and PE after hip fracture surgery were estimated at 50% and 10%, respectively. As a result, fatal PE was the most common cause of postoperative death amongst patients undergoing hip fracture surgery or total joint arthroplasty. Low-molecular-weight heparin is estimated to reduce the risk of DVT by 50% such that fatal PE is now a rare event.[2] The necessity for VTE prophylaxis in these patients cannot be overstated.

Numerous studies have investigated the efficacy and safety of UFH and LMWH after major orthopedic surgery.[2,5] Direct-acting oral anticoagulants, such as dabigatran,[9,10] rivaroxaban[11-13] and apixaban[14-16] have been compared with LMWH in patients having total joint arthroplasty. In general, DOACs are at least as effective as or slightly more effective than LMWHs to prevent VTE and have comparable safety in terms of risk of bleeding. Somewhat surprisingly, some guidelines include acetylsalicylic acid among its recommendations as a standalone option for thromboprophylaxis after major orthopedic surgery.[2] A high-quality trial of acetylsalicylic acid for thromboprophylaxis has been published in which patients having mostly hip fracture repair were enrolled.[17] This placebo-controlled study concluded that use of acetylsalicylic acid reduced rates of DVT and PE by 29%, and 43%, respectively. Cross-trial comparison would suggest that acetylsalicylic acid is less effective than LMWH and DOACs. Another high-quality trial investigated the use of acetylsalicylic acid for prophylaxis over an extended duration.[18] After an initial ten days of LMWH, patients were randomly assigned to continue on LMWH or acetylsalicylic acid for an additional 28 days. Acetylsalicylic acid was non-inferior to LMWH for the outcome of symptomatic postoperative VTE, with no significant difference in bleeding outcomes between the groups. Nevertheless, owing to poor recruitment, the trial was stopped early limiting its validity. Thus, additional study is needed before acetylsalicylic acid can be considered as a first-line standalone option for thromboprophylaxis after major orthopedic surgery, and such trials are in progress (EPCAT-II, Clinicaltrials.gov NCT01720108).

Table 4 Suggested VTE prophlyaxis options for obese patients

Agent	Non obese dosing (BMI < 30)	Suggested dosing in obesity
UFH	5,000 units *sc* bid	5,000 units *sc tid*
Enoxaparin	30 mg *sc* bid or 40 units *sc* daily	40 mg *sc bid* (BMI 40-50) 60 mg *sc bid* (BMI > 50)
Dalteparin	5,000 units *sc* daily	5,000 units *sc bid*

UFH = unfractionated heparin; BMI = body mass index

Patients having orthopedic surgery other than hip fracture repair or joint arthroplasty are at a lower risk of VTE and are studied substantially less frequently. An evidence-based approach to VTE prophylaxis among patients undergoing orthopedic surgery is presented in Table 3.

In patients having hip fracture repair or joint arthroplasty, the timing to initiate thromboprophylaxis has been the subject of debate. A recent meta-analysis found that starting thromboprophylaxis close to surgery (two hours before or within four hours after surgery) significantly increased bleeding, with a non-significant trend toward less VTE. There was no difference in efficacy or safety when thromboprophylaxis was initiated $\geq$ 12 hr either before or after surgery.[19] Importantly, a patient awaiting hip fracture surgery is at significant risk for VTE,[2] and surgical delay should prompt preoperative thromboprophylaxis while ensuring that the last dose is given at least 12 hr before surgery. Institutional VTE policies and pre-specified order sets are of particular value for reliably achieving such objectives.

Table 5 VTE prophylaxis options in patients who cannot receive UFH or LMWH

Agent	Dose	Notes
Fondaparinux	2.5 mg *sc* daily	1. tested in HFS, arthroplasty, general abdominal surgery, and medical inpatients 2. contraindicated in patients with severe renal dysfunction (CrCl < 30 mL·min^{-1}) 3. contraindicated in patients under 50 kg
Dabigatran	220 mg *po* daily	1. tested in hip and knee arthroplasty 2. contraindicated in patients with severe renal dysfunction (CrCl < 30 mL·min^{-1}) 3. 110 mg *po* dose can be used on POD 1 if given 1-4 hr postoperatively
Rivaroxaban	10 mg *po* daily	1. tested in hip and knee arthroplasty and medical inpatients 2. contraindicated in patients with severe renal dysfunction (CrCl <30 mL·min^{-1})
Apixaban	2.5 mg *po* bid	1. tested in hip and knee arthroplasty and medical inpatients 2. contraindicated in patients with severe renal dysfunction (CrCl <25 mL·min^{-1})
Acetysalicylic acid	160 mg *po* daily	1. tested adequately only in patients with HFS 2. likely less efficacious than anticoagulants
Mechanical prophylaxis		As indicated in Table 2

VTE = venous thromboembolism; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; HFS = hip fracture surgery; CrCl = creatinine clearance (calculated by Cockgroft Gault method); POD = postoperative day

Guidelines exist for the management of patients on anticoagulant drugs who have indwelling neuraxial catheters.[20,21] Neuraxial hematoma is a rare but serious complication of spinal or epidural procedures. For patients receiving postoperative epidural analgesia, antithrombotic agents should be used cautiously. In patients with indwelling spinal/epidural catheters, needle introduction should be done prior to LMWH administration; the catheter should be removed at the nadir of drug effect (just prior to next scheduled dose), and the subsequent dose should be given at least two hours after catheter removal. There is no consensus for thromboprophylaxis in the management of patients with neuraxial analgesia on DOACs. A reasonable approach consists of avoiding DOACs while a catheter is in place and delaying their administration for at least two hours after catheter removal.

The postoperative hypercoagulable state remains for up to three months following major orthopedic surgery, especially after hip replacement.[2] Prophylaxis over an extended duration for up to 35 days (including the rehabilitation/outpatient setting) reduces postoperative VTE after hip fracture repair or joint arthroplasty with no significant impact on bleeding outcomes.[2]

In the current case of a patient with a fractured hip who is to wait 24 hr for surgery, LMWH prophylaxis should be initiated immediately. A catheter for neuraxial anesthesia/analgesia can be inserted safely just prior to the operative intervention. Postoperatively, and assuming adequate hemostasis, the patient should receive LMWH for 35 days.

Case 3

A 45-yr-old obese (body mass index [BMI] 48; weight 127 kg) female is scheduled to undergo a Roux-en-Y gastric bypass for weight loss. She has severe restrictive lung disease, obstructive sleep apnea, obesity hypoventilation syndrome, and secondary pulmonary hypertension (right ventricular systolic pressure = 62 mmHg).

Obesity is a recognized risk factor for VTE.[22] Patients having bariatric surgery are at moderate to high risk for VTE with a Caprini score ≥ 4. Additionally, the presence of pre-existing pulmonary hypertension may reduce the ability for an individual to withstand the hemodynamic stress of even a small PE. Despite this, there are limited data to inform best practice for VTE prophylaxis as such patients were underrepresented or excluded from trials of LMWH. The data in this area are of low quality and recommendations are based on expert opinion. Pharmacodynamic studies have shown that anti-Xa levels are inversely related to body weight in patients receiving enoxaparin, supporting the premise of increasing prophylaxis doses of LMWH in obese patients undergoing surgery. Nevertheless, since LMWH accumulates almost entirely in the vascular space, which does not correlate linearly with total body weight, there is concern for overdosing LMWH by using dosing adjustments based on total weight.[23] Expert consensus recommends intensifying the dose of LMWH in obese patients undergoing surgery in a fixed manner (Table 4).[23] A systematic approach is needed to identify at-risk obese patients (BMI > 30 kg·m^{-2}); this would entail the use of institutional VTE policies and pre-specified order sets that incorporate preoperative BMI measurements.

The patient in this case received dalteparin 5,000 IU *sc* twice daily for the duration of her hospitalization, at ten days in total (or longer until fully ambulatory).

Case 4

A 68-yr-old male is scheduled for laparoscopic cholecystectomy due to recurrent biliary colic and recent cholangitis. He had an acute coronary syndrome 1.5 years ago that was treated with a drug-eluting stent to the left anterior descending artery. At that time, he had a severe reaction to heparin and was told that he has a "heparin allergy" and should never receive it again. He is currently receiving acetylsalicylic acid and clopidogrel, and the surgeon inquires about options for VTE prophylaxis.

Heparin-induced thrombocytopenia is an antibody-mediated reaction to heparin resulting in thrombocytopenia, bleeding, and arterial and venous thrombosis. Although not a true allergy, it is often regarded as one. Heparin-induced thrombocytopenia is fatal in 20% of unrecognized and untreated cases. It is classically described with therapeutic doses of UFH (in up to 5% of exposed surgical patients), but can also be associated with prophylactic doses of UFH and rarely any dose of LMWH. Circulating HIT antibodies persist for approximately three months. It may be safe to use heparin after this window, but expert opinion suggests the use of alternative agents in patients with a history of HIT, even if remote.[24]

Low-molecular-weight heparin and UFH are the most widely studied agents for perioperative thromboprophylaxis. For surgical patients, evidence for DOAC use is limited to hip and knee arthroplasty. Fondaparinux has been studied in medical[25] and surgical patients, both orthopedic[26-29] and nonorthopedic.[30] It is an injectable direct Xa inhibitor which, while chemically similar to LMWH, does not cross-react with or cause HIT antibodies and has been used for treatment of HIT.[31] Meta-analysis from these studies has suggested that fondaparinux has a similar efficacy profile to LMWH but causes significantly more bleeding.[32] Its use is therefore reserved for patients who are not candidates for UFH or LMWH. Table 5 provides a list of alternative thromboprophylaxis strategies.

The case above would predict a moderate to high risk of postoperative thrombosis on the basis of the patient's age and recent sepsis. His risk is low for postoperative bleeding from a laparoscopic cholecystectomy. Therefore, pharmacologic thromboprophylaxis would be indicated. Fondaparinux 2.5 mg *sc* once daily was prescribed for the duration of his hospitalization.

The presence of a drug-eluting coronary stent places this patient at increased risk for a cardiovascular event, particularly stent thrombosis, and would justify perioperative continuation of acetylsalicylic acid.[33] The perioperative management of clopidogrel is uncertain but should be interrupted five to seven days before surgery to mitigate bleeding. Although a large randomized trial compared the interruption or continuation of acetylsalicylic acid perioperatively in patients at risk for cardiovascular disease, patients with coronary stents were not adequately studied.[34] Since there is a lack of studies evaluating acetylsalicylic acid for thromboprophylaxis in non-orthopedic surgical patients, this patient should be prescribed both fondaparinux for VTE prophylaxis and acetylsalicylic acid for secondary prevention in coronary disease.

Most patients with a percutaneous coronary intervention or an acute coronary syndrome should receive dual antiplatelet therapy (DAPT) for at least one year. In selected patients, if the bleeding risk is low and thrombotic risk is high, it may be reasonable to continue both acetylsalicylic acid and a P2Y12 inhibitor (e.g., clopidogrel, ticagrelor, or prasugrel) indefinitely. As the patient in this case had his coronary event more than one year ago, there is no urgency to restart clopidogrel postoperatively, and indeed, it may be discontinued entirely at the discretion of the treating cardiologist. If the patient had his coronary event within the last year, non-urgent surgery should be deferred until approximately one year after the coronary event, at which time the P2Y12 inhibitor can be held or discontinued safely. If a patient with a coronary event within the last year needs urgent surgery (e.g., tumour resection), dual antiplatelet therapy should be continued if the anticipated increased bleeding can be managed. On the other hand, if the anticipated risk of bleeding precludes continuing both acetylsalicylic acid and a P2Y12 inhibitor perioperatively, the options would be to hold the P2Y12 inhibitor for five to seven days before the procedure or to continue DAPT and co-administer platelets at the time of the surgery. In these circumstances, consultation with both a cardiologist and a hematologist/thrombosis specialist is advisable.[35,36]

Case 5

A 75-yr-old male is scheduled for a left hemicolectomy for adenocarcinoma that will require three to five days of hospitalization. There are enlarged regional lymph nodes seen on imaging studies but no other distant metastatic disease.

In patients having subdiaphragmatic cancer surgery, their risk of VTE is increased postoperatively from baseline for approximately three months, and such patients typically have a Caprini score > 4, placing them at high risk for postoperative VTE.[2] In this population, extended-duration LMWH prophylaxis for a total of four weeks, including in the outpatient setting, is recommended by practice guidelines as it prevents excess VTE without a significant impact on bleeding complications.[5] Considerations naturally include patient preferences as self-injection and cost of drugs may have an impact on an informed decision. Enoxaparin 40 mg once daily was prescribed for this patient starting the morning after surgery for a total duration of 28 days.

Conclusions

Venous thromboembolism is a serious but preventable complication of hospitalization, especially among surgical patients. Historically, it has accounted for a high burden of postoperative morbidity and mortality. In the ERAS era, our aim should be no less ambitious than the eradication of postoperative VTE.

A systematic evidence-based approach can be achieved only through the implementation of institutional policies and utilization of standardized order sets that allow tailored thromboprophylaxis regimens. Risks of both VTE and bleeding are strongly affected by patient-specific and procedure-specific factors, and they evolve over a patient's journey through the surgical process. Enhanced Recovery After Surgery thromboprophylaxis decisions should rely on a balanced understanding of these risks.

Key points

- Appropriate strategies for VTE prophylaxis must evaluate patient, surgical, and anesthetic risks of bleeding and thrombosis.
- Low-molecular-weight heparin is the standard postoperative pharmacologic prophylactic strategy based on multiple high-quality randomized trials. Fondaparinux should be used in patients with a history of HIT or other contraindications to LMWH.
- The direct-acting oral anticoagulants, comprising dabigatran, rivaroxaban and apixaban, show efficacy and safety generally similar to LMWH in randomized trials, but they are indicated only for patients having hip or knee arthroplasty. Data for other orthopedic procedures and non-orthopedic surgical procedures are lacking.
- Duration of prophylaxis should be extended to 28-35 days for patients undergoing elective hip or knee arthroplasty, hip fracture surgery, and abdominal/pelvic cancer surgery.
- Higher doses of LMWH should be considered in patients with a BMI > 30 kg·m^{-2}.
- Venous thromboembolism was once a common postoperative complication, but effective prophylactic strategies, including both non-pharmacologic and pharmacologic means, have reduced its incidence.

Funding No direct funding was received to produce this work.

Conflict disclosures Benjamin R. Bell has received consulting fees from Sanofi-Aventis. Pascal E. Bastien has received consulting fees from Sanofi-Aventis. Benjamin R. Bell, Pascal E. Bastien, and James D. Douketis are members of Thrombosis Canada (www.thrombosiscanada.ca), a non-profit organization dedicated to knowledge translation in thrombosis medicine for Canadian health care professionals. James D. Douketis has participated in Advisory Boards for Bayer, Bristol-Myers-Squibb, Sanofi, Astra-Zeneca, Boehringer-Ingelheim, Pfizer, Biotie, Portola, and The Medicines Co.; served as a consultant for AGEN Biomedical, Ortho-Janssen Pharmaceuticals, Boehringer-Ingelheim, and Cytori; and has received grant support from Boehringer-Ingelheim. All monies from these abovementioned activities by Dr. Douketis have been deposited into university, or hospital-based research accounts.

References

1. *Kearon C*. Natural history of venous thromboembolism. Circulation 2003; 107(23 Suppl 1: I22-30.
2. *Falck-Ytter Y*, *Francis CW*, *Johanson NA*, *et al*. 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. Chest 2012; 141(2 Suppl.): e278S-325S.
3. *Stein PD*, *Matta F*, *Alrifai A*, *Rahman A*. Trends in case fatality rate in pulmonary embolism according to stability and treatment. Thromb Res 2012; 130: 841-6.
4. *Gould MK*, *Garcia DA*, *Wren SM*, *et al*. 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. Chest 2012; 141(2 Suppl.): e227S-77S.
5. *Geerts WH*, *Bergqvist D*, *Pineo GF*, *et al*. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl.): 381S-453S.
6. *Pebanco GD*, *Kaiser SA*, *Haines ST*. New pharmacologic methods to prevent venous thromboembolism in older adults: a meta-analysis. Ann Pharmacother 2013; 47: 605-16.
7. *Mauermann WJ*, *Shilling AM*, *Zuo Z*. A comparison of neuraxial block versus general anesthesia for elective total hip replacement: a meta-analysis. Anesth Analg 2006; 103: 1018-25.
8. *Caprini JA*, *Arcelus JI*, *Hasty JH*, *Tamhane AC*, *Fabrega F*. Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost 1991; 17(Suppl 3): 304-12.
9. *Eriksson BI*, *Dahl OE*, *Rosencher N*, *et al*. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost 2007; 5: 2178-85.
10. *Eriksson BI*, *Dahl OE*, *Rosencher N*, *et al*. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007; 370: 949-56.
11. *ten Cate H*, *Hamulyak K*. Rivaroxaban for thromboprophylaxis. N Engl J Med 2008; 359: 2174-6.
12. *Turpie AG*, *Lassen MR*, *Davidson BL*, *et al*. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009; 373: 1673-80.

13. *Eriksson BI*, *Kakkar AK*, *Turpie AG*, *et al*. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. J Bone Joint Surg Br 2009; 91: 636-44.
14. *Lassen MR*, *Davidson BL*, *Gallus A*, *Pineo G. J Ansell, Deitchman D*. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost 2007; 5: 2368-75.
15. *Gomez-Outes A*, *Suarez-Gea ML*, *Pozo-Hernandez C*. Apixaban or enoxaparin for thromboprophylaxis. N Engl J Med 2009; 361: 2100-1.
16. *Jameson SS*, *Sanders RD*, *Reed MR*. Apixaban vs. enoxaparin after hip replacement. N Engl J Med 2011; 364: 1177.
17. *Anonymous.* Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355: 1295-302.
18. *Anderson DR*, *Dunbar MJ*, *Bohm ER*, *et al*. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med 2013; 158: 800-6.
19. *Strebel N*, *Prins M*, *Agnelli G*, *Buller HR*. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? Arch Intern Med 2002; 162: 1451-6.
20. *Horlocker TT*, *Wedel DJ*, *Rowlingson JC*, *et al*. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 2010; 35: 64-101.
21. *Gogarten W*, *Vandermeulen E*, *Van Aken H*, *Kozek S*, *Llau JV*, *Samama CM*. Regional anaesthesia and antithrombotic agents: recommendations of the European Society of Anaesthesiology. Eur J Anaesthesiol 2010; 27: 999-1015.
22. *Goldhaber SZ*, *Savage DD*, *Garrison RJ*, *et al*. Risk factors for pulmonary embolism. The Framingham Study. Am J Med 1983; 74: 1023-8.
23. *Freeman AL*, *Pendleton RC*, *Rondina MT*. Prevention of venous thromboembolism in obesity. Exp Rev Cardiovasc Ther 2010; 8: 1711-21.
24. *Arepally GM*, *Ortel TL*. Heparin-induced thrombocytopenia. N Engl J Med 2006; 355: 809-17.
25. *Cohen AT*, *Davidson BL*, *Gallus AS*, *et al*. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006; 332: 325-9.
26. *Eriksson BI*, *Bauer KA*, *Lassen MR*, *Turpie AG*; *Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study*. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001; 345: 1298-304.
27. *Turpie AG*, *Bauer KA*, *Eriksson BI*, *Lassen MR*; *PENTATHALON 2000 Study Steering Committee*. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002; 359: 1721-6.
28. *Lassen MR*, *Bauer KA*, *Eriksson BI*, *Turpie AG*; *European Pentasaccharide Elective Surgery Study (EPHESUS) Steering Committee*. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002; 359: 1715-20.
29. *Bauer KA*, *Eriksson BI*, *Lassen MR*, *Turpie AG*; *Steering Committee of the Pentasaccharide in Major Knee Surgery Study*. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001; 345: 1305-10.
30. *Agnelli G, Bergqvist D. Cohen AT, Gallus AS, Gent M; PEGASUS Investigators.* Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg 2005; 92: 1212-20.
31. *Warkentin TE*, *Pai M*, *Sheppard JI*, *Schulman S*, *Spyropoulos AC*, *Eikelboom JW*. Fondaparinux treatment of acute heparin-induced thrombocytopenia confirmed by the serotonin-release assay: a 30-month, 16-patient case series. J Thrombosis Haemost 2011; 9: 2389-96.
32. *Eikelboom JW*, *Quinlan DJ*, *O'Donnell M*. Major bleeding, mortality, and efficacy of fondaparinux in venous thromboembolism prevention trials. Circulation 2009; 120: 2006-11.
33. *Douketis JD*, *Spyropoulos AC*, *Spencer FA*, *et al*. Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(Suppl 2): e326S-50S.
34. *Devereaux PJ*, *Mrkobrada M*, *Sessler DI*, *et al*. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014; 370: 1494-503.
35. *Spyropoulos AC*, *Albaladejo P*, *Godier A*, *et al*. Periprocedural antiplatelet therapy: recommendations for standardized reporting in patients on antiplatelet therapy: communication from the SSC of the ISTH. J Thromb Haemost 2013; 11: 1593-6.
36. *Bell AD, Roussin A, Cartier R, et al.* The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. Can J Cardiol 2011; 27 Suppl A: S1-59.