Venous Thromboembolism Prophylaxis

Jonathan Laryea, MD, FACS, FASCRS[1]   Bradley Champagne, MD, FACS, FASCRS[2]

[1] Division of Colon and Rectal Surgery, Department of surgery, University of Arkansas for Medical Sciences, Little Rock, Arkansas

[2] Division of Colon and Rectal Surgery, Department of surgery, Case Western Reserve University, Cleveland, Ohio

Address for correspondence Jonathan Laryea, MD, FACS, FASCRS, University of Arkansas for Medical Sciences, 4301 W Markham St, Slot 520, Little Rock, Arkansas 72205 (e-mail: jalaryea@uams.edu).

Abstract

Keywords

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► deep venous thrombosis
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► risk stratification

Venous thromboembolism (VTE) can occur after major general surgery. Pulmonary embolism is recognized as the most common identifiable cause of death in hospitalized patients in the United States. The risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) is higher in colorectal surgical procedures compared with general surgical procedures. The incidence of venous thromboembolism in this population is estimated to be 0.2 to 0.3%. Prevention of VTE is considered a patient-safety measure in most mandated quality initiatives. The measures for prevention of VTE include mechanical methods (graduated compression stockings and intermittent pneumatic compression devices) and pharmacologic agents. A combination of mechanical and pharmacologic methods produces the best results. Patients undergoing surgery should be stratified according to their risk of VTE based on patient risk factors, disease-related risk factors, and procedure-related risk factors. The type of prophylaxis should be commensurate with the risk of VTE based on the composite risk profile.

Objectives: On completion of this article, the reader should be able to determine risks profiles for venous thromboembolism and pulmonary embolism in patients undergoing colon and rectal surgery, and to discuss the benefits of mechanical and pharmacologic venous thromboembolism prophylaxis.

Venous thromboembolism (VTE) is common after major general surgery. The risk of VTE is estimated to be 20% for general surgical patients and 30% for patients undergoing colorectal procedures.[1] Pulmonary embolism (PE) is recognized as the most common cause of preventable hospital deaths, accounting for up to 200,000 deaths annually in the United States.[2–9] Prevention of postoperative VTE is considered a quality and patient-safety measure in most mandated quality-improvement initiatives. The Centers for Medicare and Medicaid Services (CMS) considers VTE in hospitalized patients a "never event," which is pegged to the "pay for performance" initiative.[10,11] The majority of patients who develop perioperative VTE are asymptomatic; thus, it is difficult to assess the actual incidence. Studies utilizing venography and fibrinogen uptake test have shown the incidence of deep venous thrombosis (DVT) to be up to 25%. The incidence is even higher in patients with malignancy.[12,13] Using the NSQIP database, Fleming et al showed that the postdischarge clinical incidence of DVT was 0.47 and 0.26% for PE among 52, 555 colorectal surgery patients.[14] The incidence of DVT in patients undergoing colorectal procedures is decreased by 67% with the use of perioperative prophylaxis.[15,16] Despite this, studies assessing the practice of surgeons have found that 50% of general surgery patients received incorrect VTE prophylaxis and half of these did not receive any prophylaxis at all.[17]

Interventions

Various interventions have been utilized for prophylaxis of venous thromboembolism. These include mechanical devices such as graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and pharmacologic agents such as unfractionated heparin, low-molecular-weight heparin, and fondaparinux. Most of the strategies employ a combination of mechanical methods and pharmacologic agents.

Mechanical Devices

Graduated Compression Stockings

The exact mechanism of action of GCS is not well understood. They are believed to work by compressing both the superficial

and deep venous systems, thereby increasing velocity of venous flow and also helping to empty the cusps of venous valves.[18,19] They are also believed to increase the plasma levels of tissue factor pathway inhibitor, which is a factor X_a-dependent inhibitor of the extrinsic pathway of the coagulation cascade.[20] There are two types of GCS: knee-high and thigh high.

The effectiveness of GCS in the prevention of thromboembolism has been studied extensively in the literature. A systematic review including 15 randomized control trials (RCTs) showed a 64% relative risk (RR) reduction in general surgical patients.[21] This reduction was further enhanced by combining with pharmacologic agents. In this review, there were no differences when comparing knee-high versus thigh-high GCS. In a randomized, prospective, controlled trial of 200 patients undergoing abdominal surgery, there was a 57% reduction in the incidence of deep vein thrombosis diagnosed by ^{125}I-fibrinogen test ($p < 0.025$).[22] In this study, the effectiveness of GCS was seen in patients with both benign and malignant disease. In another study of GCS in 70 patients undergoing major abdominal surgery, using GCS on one leg and using the other leg as control, DVT was diagnosed by the ^{125}I-fibrinogen test. There were 7 bilateral DVTs, 19 unilateral DVTs in the control leg, and only 1 DVT in the GCS group ($p = 0.0003$).[23] There are conflicting results with respect to whether thigh-high GCS are better than knee-high GCS. A Cochrane Review of seven RCTs including 1,027 patients, 15% of patients using GCS developed DVT compared with 29% in the control group ($p < 0.00001$). The rate of DVT decreased to 3% when GCS was combined with another method of prophylaxis compared with 14% in the control group.[24]

Intermittent Pneumatic Compression Devices

The mechanism of action of IPC devices has been studied. The sequential application of external compression on the lower extremity is believed to increase pulsatile venous flow. This leads to improved emptying of the veins thereby decreasing venous pressure resulting in an increase in arteriovenous pressure gradient and subsequent increase in arterial flow.[25] The mechanical forces applied by the IPC devices lead to shear and strain forces on the endothelial cells. This leads to enhanced antithrombotic, profibrinolytic, and vasodilatory effects, including the release of tissue plasminogen activator (tPA).[26] The increase in tPA is believed to result from a decrease in tissue plasminogen activator inhibitor 1 (tPAI-1).[27]

There are different types of IPCs. The graduated sequential compression devices produce sequential compression from distal to proximal, thereby creating a "milking" effect.[28] The uniform compression devices produce uniform compression. Both of these are equally effective in reducing the risk of DVTs.[29,30] A meta-analysis of IPC and DVT prevention in postoperative patients evaluated 15 studies including 2,270 patients. The use of IPC decreased the risk of DVT by 60% when compared with no prophylaxis (RR = 0.40, 95% confidence interval [CI], 0.29–0.56; $p < 0.001$).[31] Most of the studies have showed that a combination of IPCs with pharmacologic methods is more effective than either method alone. A Cochrane Review of 11 studies including over 7,000 patients compared mechanical compression with combination of mechanical methods and pharmacologic methods.[32] The combined modality was better than mechanical methods alone in decreasing DVT 1 versus 4% (odds ratio [OR] = 0.43; 95% CI, 0.24–0.76) and symptomatic pulmonary embolism (PE), 1 versus 3% (OR = 0.39; 95% CI, 0.25–0.63). Similarly, the combined modality was better than pharmacologic methods alone in decreasing DVT (0.65 vs. 4.21%; OR = 0.16; 95% CI, 0.07–0.34). Another Cochrane Review specifically looked at thromboprophylaxis in colorectal surgery patients.[33] This also showed that the combination of mechanical methods with low-dose heparin was better than heparin alone in preventing DVT and/ or PE (OR = 4.17; 95% CI, 1.37–12.70).

Pharmacologic Methods

Low-dose unfractionated heparin (LDUH) and low-molecular-weight heparins (LMWHs) are the main agents used for pharmacologic prophylaxis. Heparin is usually given subcutaneously as 5,000 units every 8 hours or every 12 hours. Low-molecular-weight heparins inactivate factor X_a, but they have little effect on thrombin due to their structure.[34] In the United States, LMWHs approved by the U.S. Food and Drug Administration (FDA) include enoxaparin, dalteparin, and tinzaparin. The LMWHs have different structures and pharmacologic properties; therefore, they are not interchangeable with each other or with heparin.[35,36] Fondaparinux is a synthetic pentasaccharide that binds to antithrombin, but has no effect on thrombin. It does not interact with platelets or platelet factor IV; therefore, it does not cause heparin-induced thrombocytopenia. The particular choice of pharmacologic agent often depends on pricing and hospital preferences.

Using data from the Surgical Care and Outcomes Assessment Program Collaborative Initiative of Washington State, Kwon et al evaluated the 90-day rates of death, clinically relevant VTE, and composite adverse events (CAE) in 4,195 patients.[37] There were fewer deaths (2.5 vs. 1.6%; $p = 0.03$), incidences of VTE (1.8 vs. 1.1%; $p = 0.04$), and CAE (4.2 vs. 2.5%; $p = 0.002$) in those who received pharmacologic prophylaxis.

A large multicenter study of 28 centers and over 4,000 patients evaluated the use of LDUH in preventing fatal PE.[38] In this study, patients who received LDUH had significantly fewer incidences of asymptomatic DVT, symptomatic DVT/ PE, and fatal PE when compared with controls (0.1 vs. 0.7%). One of the centers had inconsistent data; hence, the above study was reappraised to exclude data from that center. The results did not significantly differ.[39]

Multiple studies have shown that both LDUH and LMWH are equally effective in preventing DVT and PE.[40–43] A meta-analysis of LMWH versus no prophylaxis or placebo showed that LMWH decreased the risk of DVT by 72%, RR = 0.28 (95% CI, 0.14–0.54; $p < 0.001$) and clinical PE by 75%, RR = 0.25 (95% CI, 0.08–0.79; $p = 0.018$) and 71% for clinical VTE, RR = 0.29 (95% CI, 0.11–0.73; $p = 0.009$). There was no significant decrease in risk of mortality; however, there was a significant increase in bleeding complications.[44] The LMWH used in these studies included enoxaparin, dalteparin, nadroparin, tinzaparin, and Parnaparin.

Fondaparinux was compared with dalteparin in a RCT, which was designed as a noninferiority study.[45] Fondaparinux was associated with a 24.6% RR reduction in all patients, but this was not statistically significant (95% CI, –9.0–47.9; $p = 0.144$) A post hoc analysis suggested improved efficacy (RR: 40%) in reducing VTE for fondaparinux in a large subgroup of patients with malignancy. There was no significant difference in major bleeding rates.

Risk Category

The intensity of VTE prophylaxis for colorectal surgery patients should be commensurate with the estimated risk. The type of procedure and VTE risk factors determine the overall risk category. There are several published guidelines that differ substantially in the methods used to assess risk of VTE. These differences exist secondary to factors such as bias, cost, safety, efficacy, and ease of implementation. For greater than 20 years, the American College of Chest Physi-

cians (ACCP) has published extensive evidenced-based guidelines on the use of antithrombotic therapy.[46] The latest update utilizes a risk stratification model based on two previously validated risk factor point systems Rogers Score (►**Table 1**) and Caprini Score (►**Table 2**).[47–49] Furthermore, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) have each developed risk assessment guidelines for laparoscopic surgery and cancer patients, respectively. The following section outlines the evidence for risk stratification. A summary table is provided (►**Table 3**) to help categorize colorectal patients in adherence to the latest ACCP and ASCO recommendations.

The risk of VTE in colorectal surgery patients varies depending on both patient-specific and procedure-specific factors. VTE risk appears to be highest for patients undergoing abdominal or pelvic surgery for cancer and lowest for young patients undergoing ambulatory procedures.[50–53] Patient-

Table 1 Risk assessment model from the patient safety in surgery study: Rogers Score

General risk factor	Specific risk factor	Risk score points
Operation type	Respiratory	9
	Thoracoabdominal aneurysm	7
	Abdominal aneurysm	4
	Mouth, palate	4
	Stomach, small/large intestine	4
	Integument	3
	Hernia	2
ASA	3,4,5	2
	2	1
Female sex		
Work RVU	>17	3
	10–17	2
2 point conditions	Disseminated cancer	2
	Chemotherapy within 30 d	2
	Preoperative serum sodium > 145 mmol/L	2
	Transfusion > 4 units packed RBCs in 72 h within operation	2
	Ventilator dependent	2
One point conditions	Wound class 3 or 4	1
	Preoperative Hct < 38	1
	Preoperative bili > 1.0	1
	Dyspnea	1
	Albumin < 3.5	1
	Emergency	1
Zero point conditions	ASA class 1	0
	Work RVU < 10	0
	Male sex	0

Abbreviations: ASA, American Society of Anesthesiologists; Hct, hematocrit; RBCs, red blood cells; RVU, relative value update.

Table 2 Caprini risk assessment model

One point	Two points	Three points	Five points
Age 41–60 y	Age 61–74 y	Age > 75 y	Stroke (< 1 mo)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI > 25 kg/m^2	Major open surgery (> 45 min)	Factor V Leiden	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (> 45 min)	Lupus anticoagulant	Acute spinal cord injury (< 1 mo)
Varicose veins	Malignancy	Anticardiolipin antibodies	
Pregnancy or postpartum	Confined to bed (> 72 hour)	Elevated serum homocysteine	
History of spontaneous abortion	Immobilizing cast	Heparin-induced thrombocytopenia	
Oral contraceptives	Central venous access	Other congenital or acquired thrombophilia	
Sepsis (< 1 mo)			
COPD, pneumonia (< 1 mo)			
Abnormal PFTs			
Acute myocardial infarction			
Congestive heart failure			
inflammatory bowel disease			
Bed rest			

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; PFTs, pulmonary function tests; VTE, venous thromboembolism.

Table 3 Risk stratification for VTE in general gastrointestinal and abdominal-pelvic surgery

Risk category	Rogers Score	Caprini Score	Observed risk of VTE (%)	Estimated baseline risk without prophylaxis (%)
Very low	< 7	0	0	< 0.5
Low	7–10	1–2	0.7	1.5
Moderate	>10	3–4	1.0	3.0
High	NA	5 or > 5	1.9	6.0

Abbreviations: NA, not applicable; VTE, venous thromboembolism.

specific factors have been analyzed in three relatively large studies of VTE in mixed surgical populations. Independent risk factors in these studies include age > 60 years, prior VTE, and cancer[54] ; age > 60 years, prior VTE, anesthesia > 2 hours, and bed rest > 4 days[52]; older age, male sex, longer length of hospital stay, and higher Charlson Comorbidity Score[55]; and sepsis, pregnancy, or postpartum state; central venous access; malignancy; prior VTE; and inpatient hospital stay > 2 days.[56]

In another study looking at the risk related to postoperative complications, the moderate to strong independent risk factors for VTE included urinary tract infection, acute renal insufficiency, postoperative transfusion, perioperative myocardial infarction, and pneumonia.[57] Cancer patients who are scheduled to undergo colorectal surgery are a special group with a particularly high risk for VTE. Even with prophylaxis, cancer patients have a twofold higher risk for postoperative VTE compared with noncancer patients[58]; if VTE occurs, they have a threefold risk for fatal PE.[59]

Several practical and evidence-based models or guidelines exist for risk stratification. Each has limitations, but two specific models were rigorously developed, validated, and recently incorporated into the ACCP recommendations. These risk assessment scales are currently utilized by numerous academic and community hospitals in an effort to standardize evidence-based criteria for VTE prophylaxis.

The first model used data from 183,069 patients in the Patient Safety in Surgery Study. This study included patients who underwent general, vascular, and thoracic procedures at one of 128 Veterans Administration medical centers or 14 private-sector hospitals between 2002 and 2004.[47] Points were calculated for variables that were found to be independent predictors of VTE risk. The total number of points in this trial is named the *Rogers Score*. These variables include type of operation, work relative value units, several patient characteristics, and specific laboratory values (►**Table 1**). The risk of symptomatic VTE varied from very low (0.1%) to low (0.5%) to moderate (1.5%) in both development and validation studies.

This model was unique at the time of publication, but has limitations. The categories included can be cumbersome when a quick calculation is needed and the actual number of patients that received treatment during the developmental study is nebulous. Therefore, this system has largely been used to substantiate and supplement other risk-stratification models.

The second model included in the ACCP 2012 guidelines[46] also estimates VTE risk by adding points for various VTE risk factors (►Table 2).[48,49] VTE risk is categorized as being very low (0–1 point), low (2 points), moderate (3–4 points), or high (≥ 5 points). In contrast to the Rogers Score, this model (the Caprini Score) is relatively easy to use and appears to discriminate reasonably well among patients at low, moderate, and high risk for VTE. Furthermore, the Caprini Score was validated in a large retrospective study in a sample of general, vascular, and urologic surgery patients.[56] This study included a representative sample of surgical patients, avoided exclusions, minimized losses to follow-up, and had a low risk of bias. The authors also collected information about prophylaxis received. This allowed the ACCP investigators to adjust for this variable and estimate what the baseline risk of VTE would have been in the absence of prophylaxis. Although neither the Caprini Score nor the Rogers Score has yet been validated specifically in colorectal surgery, patients are similar to the abdominal and pelvic surgery patients in this trial.

The ACCP investigators also derived estimates of the baseline risk of VTE. They used the observed risks of VTE reported in the validation study by Bahlet al[57] and adjusted for prophylaxis received. The estimated baseline risks of VTE were 0.5, 1.5, 3.0 and 6.0% in patients at very low, low, moderate, and high risk for VTE, respectively (►Table 3).

Recommendations

Patients undergoing minor colorectal surgery without additional VTE risk factors, who have a Rogers Score less than 7 and Caprini Score of 0, are considered very low risk. Early and frequent ambulation is recommended in these patients without mechanical or pharmacologic prophylaxis.[46] An example would include a patient under the age of 40 undergoing a lateral internal sphincterotomy.

Patients considered low risk (Rogers Score = 7–10; Caprini Score = 1–2) benefit from mechanical prophylaxis with intermittent pneumatic compression over no prophylaxis.[46] For colorectal procedures, low risk includes noncancer patients over the age of 40, undergoing anorectal surgery with one or fewer additional risk factors.

For moderate risk colorectal patients (Rogers Score >10, Caprini Score = 3–4) the recommended approaches include pharmacologic (LDUH twice daily, LMWH, or fondaparinux) or mechanical prophylaxis with IPC. Patients not at high risk for bleeding with moderate risk for VTE should receive one of the pharmacologic agents above, while those at high risk of bleeding should use IPC.[46] Accepted risk factors for bleeding include bleeding disorders, concomitant use of clopidogrel or aspirin, renal dysfunction, conditions in which bleeding would be catastrophic, high-risk uncontrolled hemorrhage, thrombocyto-

penia, and liver disease with coagulopathy.[60] Furthermore, patients categorized as moderate risk preoperatively may fall into a higher risk category after surgery if intraoperative findings or postoperative complications change the overall score.

High-risk patients (Caprini Score ≥5), not at high risk for bleeding, should receive both pharmacologic and mechanical prophylaxis. The choice of agent (►Table 3) is typically dependent on the institution, current pathway, cost, and availability. Colorectal cancer patients are considered very high risk and thromboprophylaxis (LDUH 3 times daily, LMWH, or fondaparinux)[61] should be combined with mechanical prophylaxis. Fondaparinux (Arixtra; GlaxoSmithKline, London, UK) should be considered in colorectal cancer patients without increased bleeding risk. As outlined above, the RCT of fondaparinux versus LMWH found a significant risk reduction in VTE among patients with abdominal and pelvic cancer.[45] In addition, it is recommended that colorectal cancer patients with residual malignant disease after surgery, obese patients, or patients with histories of VTE receive extended prophylaxis (up to 4 weeks) with LMWH.[61]

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