Asian Journal of Surgery (2019) 42, 863–873

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-asianjournalsurgery.com

REVIEW ARTICLE

Venous thromboembolism in colorectal surgery: Incidence, risk factors, and prophylaxis

Shigenobu Emoto*, Hiroaki Nozawa, Kazushige Kawai, Keisuke Hata, Toshiaki Tanaka, Yasutaka Shuno, Takeshi Nishikawa, Kazuhito Sasaki, Manabu Kaneko, Masaya Hiyoshi, Koji Murono, Soichiro Ishihara

Department of Surgical Oncology, The University of Tokyo, Japan

Received 26 November 2018; accepted 25 December 2018
Available online 23 January 2019

KEYWORDS
Colorectal cancer;
Inflammatory bowel disease;
Laparoscopic surgery;
Venous thromboembolism

Summary Colorectal surgery is associated with a high risk of perioperative venous thromboembolism (VTE), and this risk is especially high following colorectal cancer resection and surgery for inflammatory bowel disease. Previous analyses of large databases have reported the incidence of postoperative VTE in this population to be approximately 1.1%–2.5%. Therefore, to minimize this risk, patients should be offered appropriate prophylaxis, which may involve a combination of mechanical and pharmacologic prophylaxis with low-dose unfractionated heparin or low molecular weight heparin as recommended by several guidelines. Prior to initiation of treatment, appropriate risk stratification should be performed according to the patients' basic and disease-related as well as procedure-related risk factors, and post-operative factors. Furthermore, a risk-benefit calculation that takes into account patients' VTE and bleeding risk should be performed prior to starting pharmacologic prophylaxis and to help determine the duration of treatment.

* Corresponding author. Department of Surgical Oncology, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan. Fax: +81 3 3811 6822.
E-mail addresses: emotos-sur@h.u-tokyo.ac.jp, shige.emt@gmail.com (S. Emoto).

https://doi.org/10.1016/j.asjsur.2018.12.013

1. Introduction

Compared to general surgery, colorectal surgery is associated with a higher risk for postoperative thromboembolic complications such as deep venous thrombosis (DVT) and pulmonary embolism (PE).[1] Among colorectal conditions, colorectal cancer (CRC) and inflammatory bowel disease (IBD) are well-known risk factors for venous thromboembolism (VTE), with an estimated incidence of VTE of 2.75%–8.9% among patients with CRC.[2–4] Among benign diseases, colorectal surgery has the highest reported incidence of VTE (734/65512, 1.12%).[5] This high risk of VTE in colorectal surgery is thought to be associated with pelvic dissection patient positioning during surgery, and the presence of additional risk factors and patient comorbidities.[6]

VTE is a common cause of preventable perioperative death. The high incidence of postoperative VTE and the availability of effective methods of prevention mandate that thromboprophylaxis be considered for all surgical patients. Surgery for colorectal disease has been drastically changing by the use of laparoscopic or robotic procedures.

In this article, we review the literature on VTE prophylaxis in colorectal surgical patients including cancer and IBD patients.

2. Incidence and risk factors for postoperative VTE in colorectal surgery

2.1. VTE incidence reported by large databases

Several large-scale studies have investigated the incidence of VTE in the United States and United Kingdom, and the results of these are summarized in Table 1.[5–19] These have reported an incidence of VTE ranging from 1.15% to 2.47%. Using data from the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) database, Henke, et al[11] reported an overall incidence of symptomatic VTE of 2.2% in colectomy patients. Important risk factors included age, body mass index (BMI), anemia, contaminated wound, surgical site infection, and sepsis/pneumonia. Notably, laparoscopic surgery was not significantly associated with VTE risk.[11] Fleming, et al[6] reported that the overall rate of 30-day VTE after colon or rectal resection was 2.47%, and the 30-day post-discharge incidence of VTE was 0.47%. Obesity, preoperative steroid use, bleeding disorder, ASA Class III, and postoperative (major and minor) complications were independently associated with an increased risk of early post-discharge VTE. In another study, the VTE rate in colorectal surgery was 2.4% (laparoscopic, 1.2%; open, 2.9%, $P < 0.001$). Open surgery, older age, steroid use, sepsis, surgical site infection, reoperation, prolonged ventilation, and low albumin were independently associated with a higher VTE rate.[7] Xenos, et al[8] reported that the incidence of VTE in CRC resection was 2.0% (open 2.2% vs laparoscopic 1.5%, $P = 0.001$). Blood transfusion, male sex, history of heart disease, emergency operation, low serum albumin, and disseminated tumor were independent predictors of VTE. Compared with Caucasian participants, Hispanic and Asian/Pacific race was independently associated with a lower risk of VTE.[8] Moghadamyeghaneh et al analyzed 219477 patients who underwent colorectal surgery from 2005 to 2013 and found a VTE incidence of 2.1%. The authors reported that 33.8% of VTE events were diagnosed after discharge. In their study, the length of postoperative hospitalization had a strong association with post-discharge VTE, with patients who were hospitalized for more than one week after an open colorectal resection having a significantly higher risk of post-discharge VTE compared to patients hospitalized for less than 4 days after a laparoscopic resection (adjusted odds ratio 12.34, $P < 0.01$).[14,18]

Using data from the Nationwide Inpatient Sample (NIS), Buchberg, et al[9] analyzed the data of 149304 patients that underwent colorectal surgery from 2002 through 2006. The overall incidence of VTE was 1.4% (laparoscopic 0.83% vs open 1.44%; $P < 0.001$). In this cohort, the IBD group experienced the highest incidence of VTE at 1.4%, followed by cancer (1.3%) and diverticulitis patients (0.9%). In the laparoscopic colectomy group, obesity, congestive heart failure, and malignancy were identified as significant risk factors for VTE. In the open colectomy group, congestive heart failure, chronic pulmonary disease, obesity, metastatic cancer, pulmonary circulation disorders, and IBD were identified as significant risk factors for VTE.[9]

In a separate study, El-Dhuweib, et al[17] investigated the incidence of VTE in England using Hospital Episode Statistics (HES) data between 2007 and 2008. They identified 35997 patients who underwent colorectal resection and reported an incidence of VTE of 2.3%. Age, postoperative stay, cancer, emergency admission, and emergency surgery for patients with IBD were independent risk factors for VTE.[17]

In the Surgical Care and Outcomes Assessment Program (SCOAP) database of Washington, the incidence of VTE after colorectal surgery was 2.2% among 16120 patients from 2006 to 2011. Pelvic operation, cancer, older age, non-elective surgery, history of VTE, and IBD were associated with an increased risk of 90-day VTE. By 2011, VTE chemoprophylaxis had increased in the perioperative setting (from 31.6% to 86.4%), in-hospital postoperative setting (from 59.6% to 91.4%), and post-discharge setting (from 8.6% to 11.7%). The 90-day VTE rate increased during this interval from 1.2% in 2006 to 3.0% in 2011.[16] Recently, Beal, et al[19] reported that the incidence of VTE after colectomy was 1.9%, with 0.7% of VTE events occurring in the post-discharge setting among 77823 cases identified from the NSQIP that underwent colectomy from 2011 to 2015.[19]

In a meta-analysis that included 11 randomized controlled trials (RCTs), Cui, et al[20] investigated the incidence of postoperative VTE in patients with colorectal cancer after laparoscopic surgery and conventional open surgery. The combined results of the individual trials showed no statistically significant difference for overall VTE (odds ratio (OR) 0.64, 95% confidence interval (CI), 0.33–1.23, $P = 0.18$); furthermore, there was no difference in subgroup analysis of DVT and anticoagulant prophylaxis between these two approaches.[20]

The studies summarized above also demonstrated that the incidence of VTE varies according to surgical site and study. For example, some studies report a lower incidence of VTE in rectal surgery compared to colon surgery,[21–23]

Table 1 Postoperative VTE incidence from large databases.

Author	Year	Country	Cohort	Database	N	Incidence of symptomatic VTE (%)	OR (95% CI) for symptomatic VTE in open surgery compared with laparoscopic surgery
Fleming[6]	2010	USA	colorectal surgery	NSQIP	52555	2.5%	1.05 (0.80—1.38)
Shapiro[7]	2011	USA	colorectal surgery	NSQIP	31109	2.4% (open 2.9%, laparoscopic 1.2%)	
Xenos[8]	2011	USA	CRC surgery	NSQIP	21943	2.0% (open 1.5%, laparoscopic 2.2%)	
Buchberg[9]	2011	USA	colorectal surgery	NIS	149304	1.4% (open 1.44%, laparoscopic 0.83%)	
Kwon[10]	2011	USA	colorectal surgery	SCOAP	4195	1.4%	1.57 (0.77—3.21)
Henke[11]	2012	USA	colectomy	NSQIP	3464	2.2% (open 2.8%, laparoscopic 1.7%)	
Wallaert[12]	2012	USA	IBD surgery	NSQIP	10431	2.3%	
Davenport[13]	2012	USA	CRC surgery	NSQIP	21943	2.0%	
Moghadamyeghaneh[14]	2014	USA	colorectal surgery	NSQIP	116029	2.0%	1.33 (1.14—1.55)
Walker[15]	2014	UK	CRC surgery	CPRD, HES, CR, ONS	4963	1.6%	
SCOAP-CERTAIN[16]	2015	USA	colorectal surgery	SCOAP	16120	2.2%	1.32 (0.84—2.08)
El-Dhuweib[17]	2016	UK	colorectal surgery	HES data	35997	2.3%	1.25 (0.74—2.09)
Moghadamyeghaneh[18]	2016	USA	colorectal surgery	NSQIP	219477	2.1%	1.36 (1.11—1.68)
Alizadeh[5]	2017	USA	laparoscopic colectomy for benign disease	NSQIP	65512	1.1%	
Beal[19]	2018	USA	colectomy	NSQIP	77823	1.9%	1.01 (0.79—1.3)

USA: the United States of America, UK: the United Kingdom, CRC: Colorectal cancer, IBD: Inflammatory bowel disease, NSQIP: National Surgical Quality Improvement Program, CPRD: the Clinical Practice Research Datalink, HES: Hospital Episode Statistics, CR: Cancer Registry, ONS: the Office for National Statistics, SCOAP: the Surgical Care and Outcomes Assessment Program, VTE: Venous thromboembolism, OR: odds ratio, CI: confidence interval.

whereas opposite results have been reported by other studies.[9]

Although the data provided from the large databases described above have contributed significantly to our understanding of VTE risk in surgical patients, these databases do have some limitations. For example, many databases lack information regarding patient characteristics including details of underlying coagulopathy, past history of VTE, and presence or absence of central venous catheters. Furthermore, accurate details of prophylaxis are also sometimes unclear.

2.2. Retrospective studies from single institutes

Retrospective studies from single institutes have been reported on various cohorts. Using CRC patient data obtained from a large database in California, a previous study reported that the risk of VTE is lower in Asians/Pacific Islanders compared to Caucasians (hazard ratio (HR) 0.4; 95% CI, 0.3—0.5).[2] However, the incidence of VTE in colorectal surgery actually varies widely from 0.2% to 4.5% in both Asian and Western countries.[22—31]

Weida, et al[29] reported that the incidence of VTE in CRC surgery was 0.5% and concluded that the risk of VTE after colorectal surgery is low in Chinese patients, and therefore colorectal surgeries for malignancy may be safely performed in this patient population without DVT prophylaxis.[22] On the other hand, Kim, et al[29] reported that the incidence of VTE was 3.7% among 840 Korean CRC patients in a single institute, while Howell et al[30] reported that VTE incidence was as high as 4% under pharmacologic prophylaxis in Australian CRC patients. Choi, et al reported that among 2006 Asian CRC patients significant predictors of VTEs were advanced stage and an increased number of co-morbidities. The two-year cumulative incidence of DVT/PE was 0.3%, 0.9% and 1.4% in stages 0—1, 2 and 3, respectively; this incidence range of DVT/PE in Asian patients with loco-regional CRC was lower than in Western patients. However, the two-year incidence (6.4%) of DVT/PE in Asian patients with distant metastases was not lower than in Western patients.[24]

The above findings suggest that several factors other than race or pharmacologic prophylaxis may affect the wide variation in VTE incidence, which may be affected by variables such as surgical procedures or postoperative protocols.

2.3. Incidence of asymptomatic VTE

The incidence of asymptomatic VTE reported in the literature is unexpectedly high. Cheung, et al[32] prospectively evaluated the incidence of postoperative DVT by duplex ultrasound of both lower limbs in 50 Chinese patients who underwent laparoscopic resection of rectal or sigmoid

cancer in the absence of thromboprophylaxis. Postoperative asymptomatic DVT occurred in 19 (38%) patients, and there were no cases of symptomatic DVT/PE. The only risk factor of asymptomatic DVT was female sex.[32] In another study from Japan, DVT was also prospectively screened with Doppler ultrasound sonography of the lower limb after laparoscopic surgery for gastric and colorectal cancer. In colorectal surgery, DVT was detected in 6 (17%) out of 35 patients. Neoadjuvant treatment (chemotherapy or chemoradiotherapy) was significantly associated with VTE.[33] In a phase II study on the efficacy and safety of VTE prophylaxis with fondaparinux in CRC patients undergoing laparoscopic surgery, the incidence rate of asymptomatic DVT was 2.5%, and the rate of symptomatic VTE was 0%.[34] In an RCT reported by Simonneau, et al[35] which compared nadroparin and enoxaparin for VTE prophylaxis after CRC surgery, the overall incidence of VTE was 14.2%, while the incidence of symptomatic VTE was 0.8% up to postoperative day 12 and 1.3% up to postoperative day 60.

The literature summarized above demonstrates that further studies are required in order to further our understanding of asymptomatic VTE risk and help stratify and therefore treat susceptible patients. Perioperative management for asymptomatic VTE should also be investigated.

2.4. VTE incidence in IBD surgery

IBD is known to be an independent risk factor for postoperative VTE. In a study of 5529 patients with Crohn's disease (CD) recruited from a Manitoba database, Bernstein, et al[36] reported that the incidence rate of DVT was 31.4/10,000 person-years while that of PE was 10.3/10,000 person-years. In ulcerative colitis (UC) the incidence rates were 30.0/10,000 person-years for DVT and 19.8/10,000 person-years for PE. The comparisons to the population cohort yielded age-adjusted incidence rate ratios (IRR) of 4.7 (95% CI, 3.5—6.3) for DVT and 2.9 (1.8—4.7) for PE in CD and 2.8 (2.1—3.7) for DVT and 3.6 (2.5—5.2) for PE in UC.[36] Using patient data from the database of National Hospital Discharge Survey in the United States, the incidence of VTE among medical patients with UC was 1.85% and relative risk compared to patients who had no IBD was 1.64. The incidence of VTE among medical patients with CD was lower than that reported for patients with UC (1.22%), while the relative risk compared with patients who did not have IBD was 1.08.[37]

Surgery further increases the risk of VTE in IBD patients. Many studies reported that VTE incidence was significantly higher in IBD surgery than in non-IBD surgery such as CRC surgery or other benign colorectal surgeries.[9,38—41] A previous study has reported that both UC (OR 1.85, 95% CI 1.70—2.01) and CD discharges (OR 1.48, 95% CI 1.35—1.62) had higher rates of VTE compared to non-IBD discharges. Moreover, the presence of bowel surgery increased the incidence of VTE in all diagnosis groups, and this was most pronounced in the UC group, in which the rate of VTE increased from 1.95% in those who did not undergo surgery to 4.23% among UC patients who underwent a colectomy.[42] Thus, VTE screening may be indicated in IBD surgery including in young patients. In other recent large studies, the VTE incidence in IBD surgery was reported as 1.2—3.8% in UC and 1.4% in CD.[12,41,43] Wallaert, et al[12] reported that bleeding disorders, steroid use, anesthesia time, emergency surgery, hematocrit <37%, malnutrition, and functional status were independent risk factors for VTE in IBD surgery.

Merrill et al[38] analyzed the NSQIP database and reported that the postoperative VTE incidence was significantly higher in IBD patients than in non-IBD patients (2.5% vs 1.0%, respectively, $P < 0.001$). Among 35997 patients who underwent colorectal resection and whose clinical details were available in the HES database, the OR for VTE risk was 2.0 (95% CI: 1.4—3.0) in IBD surgery and 2.1 (1.6—2.8) in cancer surgery, both compared with benign diseases other than IBD.[17] A recent study from the NSQIP database reported that BMI, smoking status, IBD, and hypoalbuminemia were independent risk factors for post-discharge VTE.[19]

The risk of VTE in IBD patients is further increased during an acute exacerbation. In a large database of IBD in the United Kingdom, patients with IBD had a higher risk of VTE than did controls (HR 3.4, 95% CI 2.7—4.3; $p < 0.0001$; absolute risk 2.6 per 1000 per person-years). However, during a flare-up, this increase in risk was much more prominent (8.4, 5.5—12.8; $p < 0.0001$; 9.0 per 1000 person-years).[44]

The VTE incidences were reported to be significantly lower in laparoscopic surgery than in open surgery,[7,9] though precise comparison is difficult because underlying medical co-morbidities and operative procedures vary widely. Therefore, procedures should be chosen carefully, taking patients' clinical status into full consideration.

The VTE risk in patients who had colitic cancer and IBD has not been reported. Generally, operations for colitic cancer are performed as elective procedures, while operations for IBD are often performed under emergency conditions complicated by an acute inflammatory status. Sorensen, et al[45] reported that cancer was significantly increased both in UC patients and in CD patients with VTE compared to non-IBD patients in patients with VTE in Danish national databases. These studies suggest that VTE might be a marker of occult cancer, especially young IBD patients.[45]

3. VTE prophylaxis in colorectal surgery

3.1. ACCP guideline for VTE prophylaxis

The intensity of VTE prophylaxis for colorectal surgery patients should be commensurate with the estimated risk, which is dependent upon the type of procedure and individual VTE risk factors. There are several published guidelines that differ substantially in the methods used to assess risk of VTE.[46—51] 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 Physicians (ACCP) has published extensive evidenced-based guidelines on the use of antithrombotic therapy. A summary table is provided (Table 2) to help categorize colorectal patients in adherence with the latest ACCP and the American Society of Clinical Oncology (ASCO) recommendations.[48,50] The 9th ACCP guideline decided that symptomatic VTE events should be a preferred

Table 2 Risk Stratification for VTE in abdominal-pelvic surgery (Extracted from 9th ACCP guideline).[48]

VTE risk category	Roger Score	Caprini Score	Estimated Baseline Risk in the Absence of Pharmacologic or Mechanical Prophylaxis, %	Recommendation
very low	<7	0	<0.5	Early ambulation
low	7–10	1–2	1.5	mechanical prophylaxis
moderate	>10	3–4	3	LMWH, LDUH, or mechanical prophylaxis
high	NA	>=5	6	LMWH or LDUH, and mechanical prophylaxis

LMWH: Low molecular weight heparin, LDUH: Low-dose unfractionated heparin.

outcome for evaluating the efficacy of mechanical or pharmacological prophylaxis for VTE.[48]

The risk stratification model was based on two previously validated risk factor point systems, the Rogers Score (Table 3) and Caprini Score (Table 4). The Rogers score was established using data from 183069 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.[52] This model assigned points to variables that were found to be independent predictors of VTE risk, including type of operation, work relative value units, patient characteristics, and laboratory values (Table 3). Using this model, the risk of symptomatic VTE varied from very low (0.1%) to low (−0.5%) and moderate (−1.5%) (Table 2). Unfortunately, this model is somewhat cumbersome to use. In addition, information was not provided about how many patients received prophylaxis. Another model (the Caprini score) estimates VTE risk by adding points for various VTE risk factors, as shown in Table 4.[53] VTE risk is categorized as being very low (0–1 point), low (2 points), moderate (3–4 points), or high (5- points). Although this model was not developed using rigorous statistical methods and includes some variables that were later found not to be associated with VTE risk, it is relatively easy to use and appears to discriminate reasonably well among patients at low, moderate, and high risk for VTE. Risk factors for major bleeding complications in ACCP Guideline are listed in Table 5.[48] In the absence of data from large, prospective, population-based observational studies, the baseline risk of bleeding can be derived from the control (placebo or no pharmacologic prophylaxis) groups in RCTs. However, most RCTs of pharmacoprophylaxis exclude patients who are believed to be at increased risk for bleeding. With that limitation in mind, the average baseline risk of major bleeding in the absence of prophylaxis was estimated to be 1.2% (95% CI, 0.9–1.7%) by using the pooled risk from the control groups in seven RCTs of low molecular weight heparin (LMWH) as reported in a meta-analysis.[54] The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) has also developed a risk assessment guideline for laparoscopic surgery.[55,56]

3.2. Mechanical prophylaxis for VTE

The effectiveness of graduated compression stockings (GCS) in the prevention of DVT has been studied extensively in the literature. A systematic review including 15 RCTs showed a 64% relative risk (RR) reduction in general surgical patients,[57] while a Cochrane Review of 19 RCTs including 1681 patients demonstrated that 9% of patients using GCS developed DVT compared with 21% in the control group.

Table 3 Rogers score.[52]

Risk Factor	Risk Score Points
Operation type other than endocrine	
Respiratory and hernia	9
Thoracoabdominal aneurysm, embolectomy/thrombectomy, venous reconstruction, and endovascular repair	4
Aneurysm	4
Mouth, palate	4
Stomach, intestines	4
Integument	3
Hernia	2
ASA physical status classification	
3, 4, or 5	2
2	1
Female sex	1
Work RVU	
>17	3
10–17	2
Two points for each of these conditions	2
Disseminated cancer	
Chemotherapy for malignancy within 30 d of operation	
Preoperative serum sodium >145 mmol/L	
Transfusion >4 units packed RBCs in 72 h before operation	
Ventilator dependent	
One point for each of the conditions	1
Wound class (clean/contaminated)	
Preoperative hematocrit level ≤ 38%	
Preoperative bilirubin level > 1.0 mg/dL	
Dyspnea	
Albumin level ≤ 3.5 mg/dL	
Emergency	
Zero points for each of these conditions	0
ASA physical status class 1	
Work RVU < 10	
Male sex	

ASA: the American Society of Anesthesiologists, RVU: Relative value unit, RBC: red blood cell.

Table 4 Caprini Risk Assessment Model.[53]

1 Point	2 Points	3 Points	5 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	Major open surgery (45 > min)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (>45 min)	Factor V Leiden	Acute spinal cord injury (<1 mo)
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (>72 h)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anti-cardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (<1 mo)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (<1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure (<1 mo)			
History of inflammatory bowel disease			
medical patient at bed rest			

BMI: Body mass index, VTE: Venous thromboembolism.

Table 5 Risk factors for major bleeding complications.[48]

General risk factors
Active bleeding
Previous major bleeding
Known, untreated bleeding disorder
Severe renal or hepatic failure
Thrombocytopenia
Acute stroke
Uncontrolled systolic hypertension
Lumber puncture, epidural, or spinal anesthesia within previous 4 h or next 12 h
Concomitant use of anticoagulants, antiplatelet therapy, or thrombolytic drugs
Procedure-specific risk factors
Abdominal surgery
Male sex, preoperative hemoglobin level <13 g/dL, malignancy, and complex surgery defined as two or more procedures, difficult dissection, or more than one anastomosis

The Peto odds ratio was 0.33 (95% CI 0.26–0.41) with an overall effect favoring treatment with GCS ($P < 0.00001$).[58] A meta-analysis of intermittent pneumatic compression (IPC) and DVT prevention in postoperative patients evaluated 15 studies including 2270 patients. The authors found that the use of IPC decreased the risk of DVT by 60% when compared with no prophylaxis (RR 0.40, 95% CI, 0.29–0.56; $p < 0.001$). Most of the studies conducted to date have confirmed that a combination of IPCs with pharmacologic methods is more effective than either method alone.[59] In a Cochrane Review that specifically evaluated thromboprophylaxis in colorectal surgery patients 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).[60]

In the ACCP Guideline, mechanical prophylaxis is recommended for low, moderate, and high risk category patients, and should be offered in combination with pharmacologic prophylaxis in moderate and high risk category patients.[48]

3.3. Pharmacologic prophylaxis for VTE

Pharmacological treatment is the recommended method of prophylaxis for most lower intestinal surgeries including

CRC resection and IBD surgery due to the high incidence of VTE. The ACCP guideline recommends pharmacological prophylaxis for high-risk VTE patients who are not at a high risk for bleeding.[48]

Low-dose unfractionated heparin (LDUH) and LMWHs are the main agents used for pharmacologic prophylaxis. Heparin is usually given subcutaneously as 5000 units every 8 h or every 12 h. LMWHs inactivate factor Xa, but they have little effect on thrombin due to their structure.[61]

In 1997, a large RCT conducted by the ENOXACAN Study Group proved that enoxaparin is as safe and effective as LDUH in preventing VTE in patients undergoing major elective surgery for abdominal or pelvic malignancy.[62] In 2003, a meta-analysis which analyzed 19 studies on colorectal surgery reported that heparin is effective for the prevention of VTE (OR 0.32, 95% CI 0.20—9.53), compared to no pharmacologic prophylaxis, and LDUH and LMWH were equally effective.[63]

RCTs on pharmacologic VTE prophylaxis are listed in Table 6.[21,35,62,64—67] In Singapore, 303 Asian patients undergoing elective major colorectal surgery were randomly assigned to the control or LMWH group. The incidence of DVT was significantly higher in the control group (3%) compared to the LMWH group (0%) (P = 0.045). One PE in the control group was fatal. Furthermore, bleeding-related complications were significantly higher in patients treated with LMWH.[64] McLeod, et al[21] conducted an RCT to compare the effectiveness and safety of LDUH and enoxaparin as prophylaxis against VTE after colorectal surgery. The VTE rates were the same in both groups. Although the proportion of all bleeding events in the enoxaparin group was significantly greater than in the LDUH group (10.1% vs. 6.2%, respectively, P = 0.003), the rates of major bleeding and reoperation for bleeding were not significantly different.[21] Sakon, et al[66] randomized 151 Japanese patients undergoing curative surgery for abdominal cancer to enoxaparin 20 mg twice daily for 14 days or IPC. The incidence of VTE was 1.2% (95% CI, 0.03—6.53%) in the enoxaparin group and 19.4% (95% CI, 7.45—37.47%) in the IPC group. The incidence of bleeding events was 9.2% (95% CI, 4.49—16.23%) in the enoxaparin group and 7.9% (95% CI, 1.66—21.38%) in the IPC group.[66]

In an RCT conducted by Turpie, et al,[67] the authors demonstrate that patients undergoing abdominal surgery and receiving IPC, fondaparinux 2.5 mg reduced the VTE rate by 69.8% as compared to IPC alone, with a low bleeding risk. 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. In a non-inferiority RCT, fondaparinux was compared with dalteparin. This study showed that 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.[65]

The increased risk of bleeding events must be considered in all patients given pharmacologic VTE prophylaxis. Hata, et al[68] reported the results of a prospective study that included 619 patients undergoing CRC surgery and who were administered fondaparinux, and demonstrated that the incidence of major bleeding was 0.81% (95% CI 0.3—1.9), and the incidence of minor bleeding was 9.5% (95% CI 7.3—12.1).[68] In another study of fondaparinux for colorectal cancer surgery by Yasui, et al, the incidence of major bleeding during the treatment period was 0.81% (5 of 619; 95% CI: 0.3 to 1.9). The incidence of minor bleeding was 9.5% (59 of 619). In a univariate analysis, minor bleeding occurred significantly more frequently in the laparoscopic surgery group than in the open surgery group. When all bleeding events were considered, there tended to be more events in laparoscopic surgery than in open surgery (P = 0.059), but there was no statistically significant difference between the 2 groups.[69] Other retrospective studies reported that fondaparinux was not associated with an increased risk of major bleeding, although it did increase the risk of minor bleeding.[31,70] Longer operative time was an independent risk factor for bleeding events in CRC patients undergoing laparoscopic surgery who received VTE prophylaxis by fondaparinux.[34]

The studies described above all support an important role for pharmacologic VTE prophylaxis in surgical patients, and this finding has also been validated by a number of retrospective studies.[10,28] However, a number of issues must be taken into consideration when deciding upon the most appropriate prophylactic therapy, including pricing and hospital preferences.[71] Furthermore, additional studies are still required to assess the risk of bleeding events with pharmacologic VTE prophylaxis. In particular, a bleeding risk assessment model would be clinically useful to help guide appropriate therapy.

Table 6 RCTs on pharmacologic VTE prophylaxis in colorectal surgery.

Author	Year	Indication	N	Groups	VTE, %	Bleeding, %
ENOXACAN group[62]	1997	abdominal and pelvic malignancy	1115	enoxaparin vs. LDUH	14.7/18.2[b]	4.9/2.1
Ho[64]	1999	colorectal surgery	320	enoxaparin vs. control	0/3.0[a]	6.7/1.8[a]
McLeod[21]	2001	colorectal surgery	936	LDUH vs. enoxaparin	9.4/9.4[a,b]	6.5/10.4[a]
Agnelli[65]	2005	abdominal surgery	2048	fondaparinux vs. dalteparin	4.6/6.1	3.4/2.4
Simonneau[35]	2006	CRC surgery	1288	nadroparin vs. enoxaparin	15.9/12.6[b]	7.3/11.5[a]
Sakon[66]	2010	abdominal surgery	151	enoxaparin vs. control	1.2/19.4[a,b]	9.2/7.9
Turpie[67]	2007	abdominal surgery	1309	fondaparinux vs. control	1.7/5.3[a]	1.6/0.2[a]

RCT: Randomized controlled trial, VTE: Venous thromboembolism, CRC: Colorectal cancer, LDUH: Low-dose unfractionated heparin, DVT: Deep venous thrombosis.

[a] Statistically significant.

[b] Asymptomatic DVT.

Table 7 RCTs on extended prophylaxis in abdominal surgery.

Author	Year	Indication	N	VTE (%) Control/Extended
Lausen[74]	1998	abdominal and thoracic surgery	176	10.0/5.2[a]
Bergqvist[72]	2002	abdominal and pelvic cancer surgery	332	13.8/5.5[a]
Rasmussen[75]	2006	abdominal and pelvic surgery	343	16.3/7.3[a]
Kakkar[76]	2010	abdominal and pelvic cancer surgery	488	12.1/7.7
Vedovati[77]	2014	laparoscopic CRC surgery	225	9.7/0.9[a]

RCT: Randomized controlled trial, VTE: Venous thromboembolism, CRC: Colorectal cancer.
[a] Statistically significant.

3.4. Duration of pharmacological prophylaxis

The optimal duration of pharmacological prophylaxis has been evaluated by a number of studies. Results from the NSQIP database showed that approximately one-third of postoperative VTE was diagnosed post-discharge in colorectal surgery patients.[13,18] The ENOXACAN II Study proved that enoxaparin prophylaxis for 4 weeks after surgery for abdominal or pelvic cancer is safe and significantly reduces the incidence of venographically demonstrated DVT, as compared with enoxaparin prophylaxis for one week.[72] Similarly, the ACCP guideline recommends a 4-week course of LMWH.[48]

Several RCTs investigating extended prophylaxis have also been reported (Table 7).[72–77] Vedovati, et al[77] recently reported that the incidence of VTE at 3 months after laparoscopic surgery for CRC was 9.7% and 0.9% in patients randomized to short or to extended heparin prophylaxis, respectively (relative risk reduction: 91%, 95% CI: 0.30–0.99; P = 0.005). However, several studies have questioned the cost-effectiveness of extended prophylaxis as standard for all patients.[27,30,78] For example, Verheijen, et al[25] reported that in patients undergoing laparoscopic resections for benign disease and without other risk factors have such a low VTE risk that prolonged prophylaxis is probably not warranted.[25]

Beal, et al[19] retrospectively studied the risk factors for post-discharge VTE. The authors found that the overall incidence of VTE after colectomy was 1.9%, with 0.7% of VTE events occurring in the post-discharge setting. Factors associated with post-discharge VTE risk were body mass index, preoperative albumin, operation time, hospital length of stay, race, smoking status, IBD, return to the operating room and postoperative ileus. The authors also created a prediction model for post-discharge VTE to help clinicians decide which patients would be most suitable for extended prophylaxis.[19] Further research in this area, and in particular genetic studies investigating the pathogenesis of cancer-related VTE could potentially be used to select high-risk CRC patients for thromboprophylaxis.[79]

Walker, et al[15] reported that the duration of prophylaxis after CRC resection may be guided by pathological stage and presence or absence of adjuvant chemotherapy, although Riedl, et al[80] reported that adjuvant chemotherapy was not associated with an increased risk of VTE (HR = 0.98, 95% CI 0.33–2.88), whereas disease recurrence strongly increased the risk of VTE (HR = 13.03, 95% CI 4.39–38.74).

Adherence with post-discharge VTE chemoprophylaxis is also an issue. For example, it is reported that only 1.5% of Medicare beneficiaries undergoing CRC surgery received care consistent with established guidelines for post-discharge VTE chemoprophylaxis.[81] The barriers against the extended prophylaxis may include potential patient-specific social factors, costs and insurance coverage issues and provider-prescribing patterns.[81] Treatment with oral agents may improve adherence with post-discharge VTE chemoprophylaxis. Oral edoxaban was proved to be non-inferior to subcutaneous dalteparin for the prophylaxis for recurrent VTE in cancer patients.[82] Rivaroxaban, an oral factor Xa inhibitor, was also demonstrated to be associated with a lower risk of VTE recurrence compared with dalteparin, although the rate of minor bleeding rate was higher.[83] Recently, preoperative heparin for the prevention of occult preoperative DVT was proved to be safe in major colorectal surgery.[84] Nevertheless, further trials are required to assess the optimal timing and duration of chemical thromboprophylaxis.

3.5. VTE prophylaxis in IBD surgery

There is no widely implemented standardized VTE prophylaxis or treatment practice for IBD inpatients. The ACCP guideline does not offer specific recommendations for patients with IBD, although thromboprophylaxis with LMWH, LDUH or fondaparinux are recommended in acutely ill hospitalized medical patients at increased risk for thrombosis.[48] Other guidelines on IBD recommend that pharmacologic prophylaxis should be considered depending on the patients' situation.[85–88]

Scarpa, et al[39] reported that the DVT rate in patients who underwent colorectal surgery and who had LMWH prophylaxis was higher in IBD patients than in CRC patients. They suggest that a more aggressive prophylactic therapy should be considered.[39] However, there was significant variation in practices for VTE prophylaxis in IBD patients among gastroenterologists.[89] In IBD surgery, various elements including general conditions, operative bleeding risk, and gastrointestinal bleeding risk should be carefully taken into account on a case-by-case basis to decide upon the most suitable method of VTE prophylaxis.

4. Conclusions

The risk of VTE in colorectal surgery is not insignificant, and therefore, patients should be offered appropriate

prophylaxis in order to reduce the risk of perioperative VTE. Patients undergoing colorectal surgery should be carefully stratified according to their VTE risk, taking into account risk factors, disease-related factors, and procedure-related factors. The type of prophylaxis offered should then be decided based on a risk-benefit analysis that takes into account the risk of VTE and the risk of bleeding.

Conflict of interest statement

Authors have no conflict of interest.

Funding

This research is supported by Grants-in-Aid for Scientific Research (C: grant number; 16K07143, C: grant number; 16K07161,C: grant number; 17K10620, C: grant number; 17K10621, C: grant number; 17K10623 and C: grant number; 18K07194) from Japan Society for the Promotion of Science. This research is supported by the Project for Cancer Research and Therapeutic Evolution (P-CREATE, grant number: 18cm0106502h0003 from the Japan Agency for Medical Research and Development. This work is partly supported by the Research Group for Intractable Inflammatory Bowel Disease of the Ministry of Health, Labour and Welfare of Japan (RGIBD) and Grants-in-Aid for Scientific Research (C: grant number; 17K10622).

References

1. Wille-Jorgensen P, Kjaergaard J, Jorgensen T, Korsgaard Larsen T. Failure in prophylactic management of thromboembolic disease in colorectal surgery. *Dis Colon Rectum*. 1988;31:384—386.
2. Alcalay A, Wun T, Khatri V, et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. *J Clin Oncol*. 2006;24:1112—1118.
3. Devani K, Patil N, Simons-Linares CR, et al. Trends in hospitalization and mortality of venous thromboembolism in hospitalized patients with colon cancer and their outcomes: US perspective. *Clin Colorectal Canc*. 2017;16:e199—e204.
4. Metcalf RL, Al-Hadithi E, Hopley N, et al. Characterisation and risk assessment of venous thromboembolism in gastrointestinal cancers. *World J Gastrointest Oncol*. 2017;9:363—371.
5. Alizadeh RF, Sujatha-Bhaskar S, Li S, Stamos MJ, Nguyen NT. Venous thromboembolism in common laparoscopic abdominal surgical operations. *Am J Surg*. 2017;214:1127—1132.
6. Fleming FJ, Kim MJ, Salloum RM, Young KC, Monson JR. How much do we need to worry about venous thromboembolism after hospital discharge? A study of colorectal surgery patients using the National Surgical Quality Improvement Program database. *Dis Colon Rectum*. 2010;53:1355—1360.
7. Shapiro R, Vogel JD, Kiran RP. Risk of postoperative venous thromboembolism after laparoscopic and open colorectal surgery: an additional benefit of the minimally invasive approach? *Dis Colon Rectum*. 2011;54:1496—1502.
8. Xenos ES, Vargas HD, Davenport DL. Association of blood transfusion and venous thromboembolism after colorectal cancer resection. *Thromb Res*. 2012;129:568—572.
9. Buchberg B, Masoomi H, Lusby K, et al. Incidence and risk factors of venous thromboembolism in colorectal surgery: does laparoscopy impart an advantage? *Arch Surg*. 2011;146:739—743.
10. Kwon S, Meissner M, Symons R, et al. Perioperative pharmacologic prophylaxis for venous thromboembolism in colorectal surgery. *J Am Coll Surg*. 2011;213:596—603, 603 e591.
11. Henke PK, Arya S, Pannucci C, et al. Procedure-specific venous thromboembolism prophylaxis: a paradigm from colectomy surgery. *Surgery*. 2012;152:528—534. discussion 534-526.
12. Wallaert JB, De Martino RR, Marsicovetere PS, et al. Venous thromboembolism after surgery for inflammatory bowel disease: are there modifiable risk factors? Data from ACS NSQIP. *Dis Colon Rectum*. 2012;55:1138—1144.
13. Davenport DL, Vargas HD, Kasten MW, Xenos ES. Timing and perioperative risk factors for in-hospital and post-discharge venous thromboembolism after colorectal cancer resection. *Clin Appl Thromb Hemost*. 2012;18:569—575.
14. Moghadamyeghaneh Z, Hanna MH, Carmichael JC, Nguyen NT, Stamos MJ. A nationwide analysis of postoperative deep vein thrombosis and pulmonary embolism in colon and rectal surgery. *J Gastrointest Surg*. 2014;18:2169—2177.
15. Walker AJ, West J, Card TR, Humes DJ, Grainge MJ. Variation in the risk of venous thromboembolism in people with colorectal cancer: a population-based cohort study from England. *J Thromb Haemostasis*. 2014;12:641—649.
16. Colorectal Writing Group for Surgical Care and Outcomes Assessment Program—Comparative Effectiveness Research Translation Network (SCOAP-CERTAIN) Collaborative, Nelson DW, Simianu VV, et al. Thromboembolic complications and prophylaxis patterns in colorectal surgery. *JAMA Surg*. 2015;150:712—720.
17. El-Dhuwaib Y, Selvasekar C, Corless DJ, Deakin M, Slavin JP. Venous thromboembolism following colorectal resection. *Colorectal Dis*. 2017;19:385—394.
18. Moghadamyeghaneh Z, Alizadeh RF, Hanna MH, et al. Post-hospital discharge venous thromboembolism in colorectal surgery. *World J Surg*. 2016;40:1255—1263.
19. Beal EW, Tumin D, Chakedis J, et al. Which patients require extended thromboprophylaxis after colectomy? modeling risk and assessing indications for post-discharge pharmacoprophylaxis. *World J Surg*. 2018;42:2242—2251.
20. Cui G, Wang X, Yao W, Li H. Incidence of postoperative venous thromboembolism after laparoscopic versus open colorectal cancer surgery: a meta-analysis. *Surg Laparosc Endosc Percutaneous Tech*. 2013;23:128—134.
21. McLeod RS, Geerts WH, Sniderman KW, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. *Ann Surg*. 2001;233:438—444.
22. Weida D, Patrick LY, Andrew YW. Is it safe to perform operation for colorectal malignancy in Chinese patients without DVT prophylaxis? An 8-year experience from a regional hospital in Hong Kong. *Chin Med J (Engl)*. 2010;123:1973—1975.
23. Yang SS, Yu CS, Yoon YS, Yoon SN, Lim SB, Kim JC. Symptomatic venous thromboembolism in Asian colorectal cancer surgery patients. *World J Surg*. 2011;35:881—887.
24. Choi S, Lee KW, Bang SM, et al. Different characteristics and prognostic impact of deep-vein thrombosis/pulmonary embolism and intraabdominal venous thrombosis in colorectal cancer patients. *Thromb Haemostasis*. 2011;106:1084—1094.
25. Verheijen PM, Stevenson AR, Stitz RW, Clark DA, Clark AJ, Lumley JW. Prolonged use of thromboprophylaxis may not be necessary in laparoscopic colorectal surgery. *Int J Colorectal Dis*. 2011;26:755—759.
26. Monn MF, Haut ER, Lau BD, et al. Is venous thromboembolism in colorectal surgery patients preventable or inevitable? One institution's experience. *J Am Coll Surg*. 2013;216:395—401 e391.
27. Chandra R, Melino G, Thomas M, Lawrence MJ, Hunter RA, Moore J. Is extended thromboprophylaxis necessary in elective colorectal cancer surgery? *ANZ J Surg*. 2013;83:968—972.

28. Erem HH, Kiran RP, Remzi FH, Vogel JD. Venous thromboembolism in colorectal surgery: skip SCIP or comply? *Tech Coloproctol*. 2014;18:719—724.
29. Kim DS, Park KM, Won YS, et al. Occurrence and prognosis of symptomatic venous thromboembolism in colorectal cancer surgery patients. *Vasc Specialist Int*. 2014;30:49—55.
30. Holwell A, McKenzie JL, Holmes M, et al. Venous thromboembolism prevention in patients undergoing colorectal surgery for cancer. *ANZ J Surg*. 2014;84:284—288.
31. Yamaoka Y, Ikeda M, Ikenaga M, Haraguchi N, Miyake M, Sekimoto M. Safety and efficacy of fondaparinux for prophylaxis of venous thromboembolism after colorectal cancer resection: a propensity score matched analysis. *Dig Surg*. 2015; 32:190—195.
32. Cheung HY-S, Chung C-C, Yau KK-K, et al. Risk of deep vein thrombosis following laparoscopic rectosigmoid cancer resection in Chinese patients. *Asian J Surg*. 2008;31:63—68.
33. Kimura Y, Oki E, Ando K, Saeki H, Kusumoto T, Maehara Y. Incidence of venous thromboembolism following laparoscopic surgery for gastrointestinal cancer: a single-center, prospective cohort study. *World J Surg*. 2016;40:309—314.
34. Tokuhara K, Matsushima H, Ueyama Y, Nakatani K, Yoshioka K, Kon M. Efficacy and safety of thromboembolism prophylaxis with fondaparinux in Japanese colorectal cancer patients undergoing laparoscopic surgery: a phase II study. *Int J Surg*. 2017;42:203—208.
35. Simonneau G, Laporte S, Mismetti P, et al. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer. *J Thromb Haemostasis*. 2006;4:1693—1700.
36. Bernstein CN, Blanchard JF, Houston DS, Wajda A. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemostasis*. 2001;85:430—434.
37. Saleh T, Matta F, Yaekoub AY, Danescu S, Stein PD. Risk of venous thromboembolism with inflammatory bowel disease. *Clin Appl Thromb Hemost*. 2011;17:254—258.
38. Merrill A, Millham F. Increased risk of postoperative deep vein thrombosis and pulmonary embolism in patients with inflammatory bowel disease: a study of National Surgical Quality Improvement Program patients. *Arch Surg*. 2012;147:120—124.
39. Scarpa M, Pilon F, Pengo V, et al. Deep venous thrombosis after surgery for inflammatory bowel disease: is standard dose low molecular weight heparin prophylaxis enough? *World J Surg*. 2010;34:1629—1636.
40. Ramirez JI, Vassiliu P, Gonzalez-Ruiz C, et al. Sequential compression devices as prophylaxis for venous thromboembolism in high-risk colorectal surgery patients: reconsidering American Society of Colorectal Surgeons parameters. *Am Surg*. 2003;69:941—945.
41. Wang JY, Terdiman JP, Vittinghoff E, Minichiello T, Varma MG. Hospitalized ulcerative colitis patients have an elevated risk of thromboembolic events. *World J Gastroenterol*. 2009;15(8).
42. Nguyen GC, Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol*. 2008; 103:2272—2280.
43. O'Connor OJ, Cahill RA, Kirwan WO, Redmond HP. The incidence of postoperative venous thrombosis among patients with ulcerative colitis. *Ir J Med Sci*. 2005;174:20—22.
44. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet*. 2010;375:657—663.
45. Sorensen GV, Erichsen R, Svaerke C, Farkas DK, Sorensen HT. Risk of cancer in patients with inflammatory bowel disease and venous thromboembolism: a nationwide cohort study. *Inflamm Bowel Dis*. 2012;18:1859—1863.
46. Group JCSJW. Guidelines for the diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis (JCS 2009). *Circ J*. 2011;75:1258—1281.
47. Mandala M, Falanga A, Roila F, Group EGW. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2011;22: vi85—vi92.
48. 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:e227S—e277S.
49. Farge D, Debourdeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemostasis*. 2013;11:56—70.
50. Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American society of clinical Oncology clinical practice guideline update 2014. *J Clin Oncol*. 2015;33:654—656.
51. Streiff MB, Holmstrom B, Ashrani A, et al. Cancer-associated venous thromboembolic disease, version 1.2015. *J Natl Compr Canc Netw*. 2015;13:1079—1095.
52. Rogers Jr SO, Kilaru RK, Hosokawa P, Henderson WG, Zinner MJ, Khuri SF. Multivariable predictors of postoperative venous thromboembolic events after general and vascular surgery: results from the patient safety in surgery study. *J Am Coll Surg*. 2007;204:1211—1221.
53. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon*. 2005;51:70—78.
54. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg*. 2001;88:913—930.
55. Society of American G, Endoscopic Surgeons Guidelines C. Guidelines for deep venous thrombosis prophylaxis during laparoscopic surgery. *Surg Endosc*. 2007;21:1007—1009.
56. Richardson WS, Hamad GG, Stefanidis D, Committee SG. SAGES VTE prophylaxis for laparoscopic surgery guidelines: an update. *Surg Endosc*. 2017;31:501—503.
57. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. *Br J Surg*. 1999; 86:992—1004.
58. Sachdeva A, Dalton M, Amaragiri SV, Lees T. Graduated compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev*. 2014;12:CD001484.
59. Urbankova J, Quiroz R, Kucher N, Goldhaber SZ. Intermittent pneumatic compression and deep vein thrombosis prevention. A meta-analysis in postoperative patients. *Thromb Haemostasis*. 2005;94:1181—1185.
60. Wille-Jørgensen P, Rasmussen MS, Andersen BR, Borly L. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. *Cochrane Database Syst Rev*. 2003;(4): CD001217.
61. Weitz JI. Low-molecular-weight heparins. *N Engl J Med*. 1997; 337:688—698.
62. Group ES. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group. *Br J Surg*. 1997;84:1099—1103.
63. Wille-Jorgensen P, Rasmussen MS, Andersen BR, Borly L. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. *Cochrane Database Syst Rev*. 2003: CD001217.
64. Ho YH, Seow-Choen F, Leong A, Eu KW, Nyam D, Teoh MK. Randomized, controlled trial of low molecular weight heparin vs. no deep vein thrombosis prophylaxis for major colon and

rectal surgery in Asian patients. *Dis Colon Rectum*. 1999;42:196—202. discussion 202-193.
65. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M, investigators P. 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—1220.
66. Sakon M, Kobayashi T, Shimazui T. Efficacy and safety of enoxaparin in Japanese patients undergoing curative abdominal or pelvic cancer surgery: results from a multicenter, randomized, open-label study. *Thromb Res*. 2010;125:e65—e70.
67. Turpie AG, Bauer KA, Caprini JA, et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. *J Thromb Haemostasis*. 2007;5:1854—1861.
68. Hata T, Yasui M, Murata K, et al. Safety of fondaparinux to prevent venous thromboembolism in Japanese patients undergoing colorectal cancer surgery: a multicenter study. *Surg Today*. 2014;44:2116—2123.
69. Yasui M, Ikeda M, Miyake M, et al. Comparison of bleeding risks related to venous thromboembolism prophylaxis in laparoscopic vs open colorectal cancer surgery: a multicenter study in Japanese patients. *Am J Surg*. 2017;213:43—49.
70. Tsutsumi S, Yajima R, Tabe Y, et al. The efficacy of fondaparinux for the prophylaxis of venous thromboembolism after resection for colorectal cancer. *Hepato-Gastroenterology*. 2012;59:2477—2479.
71. Laryea J, Champagne B. Venous thromboembolism prophylaxis. *Clin Colon Rectal Surg*. 2013;26:153—159.
72. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med*. 2002;346:975—980.
73. Sammour T, Chandra R, Moore JW. Extended venous thromboembolism prophylaxis after colorectal cancer surgery: the current state of the evidence. *J Thromb Thrombolysis*. 2016;42:27—32.
74. Lausen I, Jensen R, Jorgensen LN, et al. Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. *Eur J Surg*. 1998;164:657—663.
75. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study. *J Thromb Haemostasis*. 2006;4:2384—2390.
76. Kakkar VV, Balibrea JL, Martinez-Gonzalez J, Prandoni P, Group CS. Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study. *J Thromb Haemostasis*. 2010;8:1223—1229.
77. Vedovati MC, Becattini C, Rondelli F, et al. A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer. *Ann Surg*. 2014;259:665—669.
78. Vendler MMI, Haidari TA, Waage JE, et al. Incidence of venous thromboembolic events in enhanced recovery after surgery for colon cancer: a retrospective, population-based cohort study. *Colorectal Dis*. 2017;19:O393—O401.
79. Unlu B, van Es N, Arindrarto W, et al. Genes associated with venous thromboembolism in colorectal cancer patients. *J Thromb Haemostasis*. 2018;16:293—302.
80. Riedl JM, Posch F, Bezan A, et al. Patterns of venous thromboembolism risk in patients with localized colorectal cancer undergoing adjuvant chemotherapy or active surveillance: an observational cohort study. *BMC Canc*. 2017;17:415.
81. Merkow RP, Bilimoria KY, Sohn MW, et al. Adherence with postdischarge venous thromboembolism chemoprophylaxis recommendations after colorectal cancer surgery among elderly Medicare beneficiaries. *Ann Surg*. 2014;260:103—108.
82. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378:615—624.
83. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36:2017—2023.
84. Zaghiyan KN, Sax HC, Miraflor E, et al. Timing of chemical thromboprophylaxis and deep vein thrombosis in major colorectal surgery. *Ann Surg*. 2016;264:632—639.
85. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut*. 2011;60:571—607.
86. Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of G. Ulcerative colitis practice guidelines in adults: American College of gastroenterology, practice parameters committee. *Am J Gastroenterol*. 2010;105:501—523. quiz 524.
87. Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis*. 2010;4:63—101.
88. Travis SP, Stange EF, Lemann M, et al. European evidence-based Consensus on the management of ulcerative colitis: current management. *J Crohns Colitis*. 2008;2:24—62.
89. Sam JJ, Bernstein CN, Razik R, Thanabalan R, Nguyen GC. Physicians' perceptions of risks and practices in venous thromboembolism prophylaxis in inflammatory bowel disease. *Dig Dis Sci*. 2013;58:46—52.