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CONSENSUS STATEMENT

Consensus Statements on the Risk, Prevention, and Treatment of Venous Thromboembolism in Inflammatory Bowel Disease: Canadian Association of Gastroenterology

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BACKGROUND & AIMS: Guidelines for the management of venous thromboembolism (VTE) from the American College of Chest Physicians do not address patients with inflammatory bowel disease (IBD), a group with a high risk of both VTE and gastrointestinal bleeding. We present recommendations for the prevention and treatment of VTE in patients with IBD. **METHODS:** A systematic literature search was performed to identify studies on VTE in IBD. The quality of evidence and strength of recommendations were rated according to the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach. Statements were developed through an iterative online platform, then finalized and voted on by a working group of adult and pediatric gastroenterologists and thrombosis specialists. **RESULTS:** IBD patients have an approximately 3-fold higher risk of VTE compared with individuals without IBD, and disease flares further increase this risk. Anticoagulant thromboprophylaxis is recommended for IBD patients who are hospitalized with IBD flares without active bleeding and is suggested when bleeding is nonsevere. Anticoagulant thromboprophylaxis is suggested during moderate–severe IBD flares in outpatients with a history of VTE provoked by an IBD flare or an unprovoked VTE, but not otherwise. The recommended duration of anticoagulation after a first VTE is based on the presence of provoking factors. Specific suggestions are made for the prevention and treatment of VTE in pediatric and pregnant IBD patients. **CONCLUSIONS:** Using the American College of Chest Physicians' guidelines as a foundation, we have integrated evidence from IBD studies to develop specific recommendations for the management of VTE in this high-risk population.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Venous Thromboembolism; Anticoagulant Therapy.

In 2012, the American College of Chest Physicians (ACCP) developed guidelines for the prevention and treatment of venous thromboembolism (VTE)[1,2] in adults, children, and pregnant women.[3–7] In the 2008 iteration of the ACCP guidelines,[8] inflammatory bowel disease (IBD) was specifically mentioned as a risk factor for VTE, but this was not the case in the 2012 edition. Substantial data suggest that IBD is indeed a risk factor for VTE, with a 3-fold higher risk compared with patients without IBD.[9–11] Although surveys of gastroenterologists from the United States and Canada indicate that physicians recognize this increased risk, there remain areas of uncertainty regarding the management of VTE in IBD patients, including the use of prophylaxis in patients admitted to hospital for non-IBD conditions and duration of anticoagulation when VTE occurs.[12,13]

The purpose of these consensus statements is to review the literature relating to VTE and IBD and to develop specific recommendations applicable to this patient group.

Methods

Scope and Purpose

The purpose of this consensus statement is to develop specific recommendations for the prevention and treatment of

Abbreviations used in this paper: **ACCP, American College of Chest Physicians; CAG, Canadian Association of Gastroenterology; CD, Crohn's disease; CI, confidence interval; DVT, deep venous thrombosis; GRADE, Grading of Recommendation Assessment, Development and Evaluation; HR, hazard ratio; IBD, inflammatory bowel disease; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; OR, odds ratio; QALY, quality-adjusted life years; UC, ulcerative colitis; VTE, venous thromboembolism.**

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VTE in patients with IBD. The specific questions to be addressed were identified by the participants and aided by a review of the IBD literature and the recent ACCP guidelines (Figure 1).

Sources and Searches

A systematic literature search was performed by the Editorial Office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University. MEDLINE (1946 to October 2012), EMBASE (1980 to October 2012), and CENTRAL (Cochrane Central Register of Controlled Trials, Issue 10, 2012) were searched for relevant studies. Key search terms included *Crohn's disease*, *ulcerative colitis*, *inflammatory bowel disease*, *venous thromboembolism*, *anticoagulant agent* (eg, heparin and other specific agents), *intermittent pneumatic compression*, and *graduated compression stockings*. The search was limited to human studies and the English language. The search strategies used for Medline and EMBASE are shown in Supplementary Table 1. Additional manual searches of these databases were conducted up to June 2013.

Review and Grading of Evidence

The quality of evidence was assessed according to the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach.[14] The assessment was performed by 2 methodologists (Dr Grigorios Leontiadis and Dr Paul Moayyedi) who did not participate in the statement voting process. One methodologist determined the risk of bias ("methodological quality") of individual studies supporting each statement, the risk of bias across studies for each statement, and the overall quality of evidence across studies for each statement. The second methodologist reviewed the assessments and disagreements were resolved by consensus. The assessments were subsequently reviewed and agreed on by the voting members of the guidelines committee.

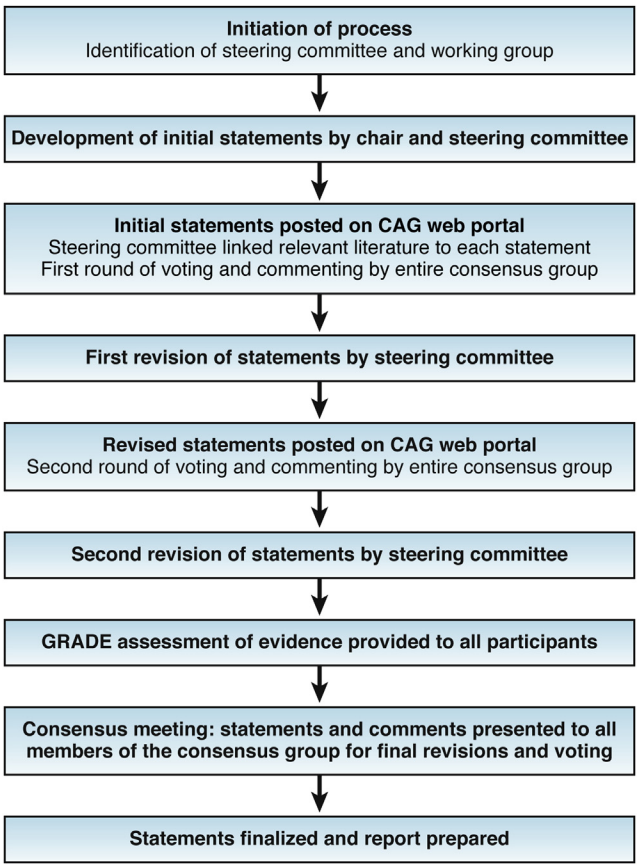

Figure 1. Guideline development process.

The quality of evidence for each consensus statement was classified as high, moderate, low, or very low. Evidence from randomized controlled trials started as high quality, but was downgraded if there was high risk of bias across studies, inconsistency (heterogeneity) of findings among studies, indirectness of the evidence (eg, in relationship to the study population, intervention, or outcomes), imprecision of findings, or evidence of reporting bias. Evidence from case-control or cohort studies started as low quality and could be further downgraded for the criteria mentioned, or could be upgraded if the treatment effect was very large, if there was a dose–response relationship, or if all plausible biases were expected to decrease the treatment effect.[14]

Consensus Process

The multidisciplinary consensus group included 13 voting participants with expertise in the areas of gastroenterology, respirology, hematology, and pediatrics, and a nonvoting facilitator.

Working subgroups and the meeting chair developed initial statements. A web-based consensus platform (ECD Solutions, Atlanta, GA) supported by the Canadian Association of Gastroenterology (CAG) was used to facilitate most aspects of the consensus process before the final face-to-face meeting. Via the consensus platform, the working groups reviewed the results of initial literature searches and identified relevant references, which were then "tagged" (selected and linked) to the each statement; used a modified Delphi process to vote anonymously on their level of agreement with the statements; suggested revisions to statements; and provided comments on specific references and background data. Statements were progressively revised through 2 separate voting/commenting iterations and finalized at the consensus meeting. All participants had access to all abstracts, electronic copies of the individual "tagged" references, and the GRADE evaluations of the evidence for each statement.

The group held a 1-day consensus conference in June 2013, where data were presented, wording of the statements was discussed and finalized, and participants voted on their level of agreement with each statement on a scale of 1 to 6 (1 = disagree strongly, 2 = disagree with major reservations, 3 = disagree with minor reservations, 4 = agree with major reservations, 5 = agree with minor reservations, and 6 = agree strongly). A statement was accepted if >75% of participants voted 4, 5, or 6. The strength of recommendation was also finalized by consensus. According to the GRADE approach, there are 2 categories for strength of recommendations: strong recommendations ("we recommend . . .") and weak recommendations ("we suggest . . ."). For clinicians, a strong recommendation means that they should follow this course of action in treating most patients, and a weak recommendation means that they ". . . should recognize that different choices will be appropriate for different patients and that they must help each patient to arrive at a management decision consistent with her

or his values and preferences."[15] It is important to note that the quality of evidence is only 1 of 4 determinants of the strength of recommendations. The other 3 determinants are (1) balance between risks and benefits; (2) patients' values and preferences; and (3) cost and resource allocation.[15] This means that it is possible for recommendations to be issued as strong even if there is low quality of evidence and, inversely, for recommendations to be issued as weak when the quality of evidence is high. A working group drafted the manuscript, which was then reviewed and approved by all participants.

In accordance with CAG policies, financial conflicts of interest within the 24 months before the consensus meeting were declared in writing by, and were available to, all voting participants.

Role of the Funding Sources

The conference was funded by unrestricted grants to the CAG from AbbVie Canada and Warner Chilcott. The CAG administered all aspects of the meeting, and the funding sources had no role in the drafting or approval of these guidelines.

Recommendation Statements

Each recommendation statement is followed by the GRADE of supporting evidence, the result of the vote, and a discussion of the evidence. Table 1 summarizes the recommendation statements, and Supplementary Table 2 provides a summary of the relevant ACCP recommendations.[2–6] The term *anticoagulant thromboprophylaxis* refers to any anticoagulant-based method of VTE prophylaxis (ie, any approved type and dose of anticoagulant). A recommendation for anticoagulant prophylaxis indicates that prophylaxis should be used and that an anticoagulant is preferable to mechanical prophylaxis. When there is a need to specify the type of anticoagulant regimen, we have done so (eg, low-molecular-weight heparin [LMWH] or low-dose unfractionated heparin).

Background Statements

Statement 1: Overall, inflammatory bowel disease (IBD) patients have about a 3-fold higher risk of venous thromboembolism (VTE) compared with the general population, with the absolute risk being much higher in the hospital setting compared with the nonhospital setting. *GRADE: low-quality evidence. Vote: agree strongly 92%; agree with minor reservations 8%.* Large population-based studies have shown that the risks of both pulmonary embolism (PE) and deep venous thrombosis (DVT) are several-fold higher in patients with IBD compared with the general population.[16,17] A meta-analysis of 11 case-control and cohort studies estimated the relative risk for DVT and PE among IBD patients to be 2.20 (95% confidence interval [CI]: 1.83−2.65) compared with non-IBD subjects (ulcerative colitis [UC] = 2.57; 95% CI: 2.02−3.28 and Crohn's disease [CD] = 2.12; 95% CI: 1.40−3.20).[17] However, there was substantial heterogeneity among the identified studies, with some including only hospitalized IBD patients, and others including only pregnant women with IBD.

Three of the studies were large, population-based, retrospective cohort studies, which best reflect the risk of VTE in the entire population with the least risk of selection bias.[9–11] Each of these 3 studies yielded relative risk estimates for VTE by comparing IBD patients with age- and sex-matched non-IBD controls. We performed a meta-analysis of data from these studies, which revealed a 2.85-fold increased risk of VTE in IBD patients as summarized in Figure 2.

The absolute risk is reportedly much higher in the hospital vs the nonhospital setting. In a UK cohort study, the absolute risk of VTE in IBD patients was 25.2/1000 person-years during hospitalized periods compared with 1.8/1000 person-years during ambulatory periods.[10]

Statement 2: Moderate−severe disease activity is an important factor that drives the increased risk of VTE in IBD and should be considered a provoking factor. *GRADE: low-quality evidence. Vote: agree strongly 92%; agree with minor reservations 8%.* Between 60% and 80% of IBD patients have active disease when they develop VTE.[10,18–21] A large UK cohort study showed that the risk of VTE among IBD patients compared with the general population was higher during acute flares (hazard ratio [HR] = 8.4; 95% CI: 5.5−12.8) compared with periods of remission (HR = 2.1; 95% CI: 1.6−2.9).[10] The relative risks during flare and remission compared with the general population were higher during nonhospitalized (HR = 15.8 and 2.2) than hospitalized periods (HR = 3.2 and 1.7). The relative incidence of VTE during periods of flares compared with remission was 4.5 (95% CI: 2.6−7.8) and was most pronounced in the ambulatory setting (incidence rate ratio = 8.7; 95% CI: 4.4−16.9). This study defined acute flare through the use of oral corticosteroids, an imprecise surrogate indicator of disease activity. Because oral corticosteroids are typically prescribed for the treatment of moderate−severe IBD, we broadly interpret acute flare to include those of at least moderate−severe disease activity and not mild flares.

Moderate−severe disease activity might also be identified by symptom-based activity indices, such as the Harvey-Bradshaw Index and the modified Mayo Index, which are frequently used for CD and UC, respectively (Supplementary Tables 3 and 4).[22–24] Although these indices provide a framework for measuring disease activity, an experienced physician's global rating (ie, remission, mild, moderate, severe) is also sufficient for risk stratification.

Statement 3: The risk of VTE during a hospitalized IBD flare is estimated to be 6-fold higher than during a nonhospitalized flare. *GRADE: low-quality evidence. Vote: agree strongly 70%; agree with minor reservations 30%.* In the large UK cohort study, the absolute risk of VTE during a moderate−severe flare was 38/1000 person-years among hospitalized IBD patients compared with 6/1000 person-years among ambulatory patients.[10] To place this into perspective, these rates can be compared with those associated with cancer, a recognized

Table 1. Summary of consensus recommendations for the prevention and management of VTE in patients with IBD

Background statements	Consistency with ACCP[2–6]
1: Overall, IBD patients have about a 3-fold higher risk of VTE compared with the general population, with the absolute risk being much higher in the hospital setting compared with the nonhospital setting. **GRADE: low-quality evidence**	Not applicable
2: Moderate–severe disease activity is an important factor that drives the increased risk of VTE in IBD and should be considered a provoking factor. **GRADE: low-quality evidence**	Not applicable
3: The risk of VTE during a hospitalized IBD flare is estimated to be 6-fold higher than during a nonhospitalized flare. **GRADE: low-quality evidence**	Not applicable
Recommendations for prevention of VTE	ACCP
4: For IBD patients who are hospitalized with moderate–severe IBD flares without severe bleeding, we recommend anticoagulant thromboprophylaxis with LMWH, low-dose unfractionated heparin, or fondaparinux over no prophylaxis. **GRADE: Strong recommendation, low-quality evidence**	Consistent
5: For IBD patients who are hospitalized for indications unrelated to their IBD, including those in clinical remission, we suggest anticoagulant thromboprophylaxis. **GRADE: Weak recommendation, low-quality evidence**	Not addressed
6: For hospitalized IBD patients with nonsevere gastrointestinal bleeding related to their disease, we suggest anticoagulant thromboprophylaxis. **GRADE: Weak recommendation, low-quality evidence**	Discordant
7a: For hospitalized IBD patients who have severe IBD-related gastrointestinal bleeding, we suggest mechanical thromboprophylaxis (preferably IPC) over no prophylaxis. **GRADE: Weak recommendation, low-quality evidence**	Consistent
7b: If bleeding becomes no longer severe, we suggest anticoagulant thromboprophylaxis be substituted for mechanical thromboprophylaxis. **GRADE: Weak recommendation, low-quality evidence**	Consistent
8: For IBD patients who have undergone major abdominal-pelvic or general surgery, we recommend anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. **GRADE: Strong recommendation, moderate-quality evidence**	Consistent
9: In outpatients presenting with an IBD flare who have not had a previous VTE, we recommend against anticoagulant thromboprophylaxis. **GRADE: Strong recommendation, low-quality evidence**	Not addressed
10: For IBD outpatients with a previous VTE who are no longer on anticoagulation, we suggest anticoagulant thromboprophylaxis during moderate-severe IBD flares unless all previous episodes of VTE occurred after major surgery. **GRADE: Weak recommendation, very low-quality evidence**	Not addressed
11: For pediatric IBD patients (younger than 18 years of age) without a previous VTE who are admitted for an IBD flare, we suggest against anticoagulant thromboprophylaxis. **GRADE: Weak recommendation, low-quality evidence**	Not addressed
12: For pregnant women with IBD who have undergone cesarean section, we suggest anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. **GRADE: Weak recommendation, low-quality evidence**	Consistent
13: In patients with VTE, coexisting IBD is not an indication for testing for hereditary or acquired hypercoagulable states. **GRADE: Strong recommendation, very low-quality evidence**	Not addressed
14: For IBD patients who are diagnosed with their first episode of VTE while in clinical remission and in the absence of another provoking factor, we suggest indefinite anticoagulant therapy with periodic review of this decision. **GRADE: Weak recommendation, very low-quality evidence**	Not addressed
15a: For patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. **GRADE: Strong recommendation, very low-quality evidence**	Consistent
15b: For IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy. **GRADE: Weak recommendation, very low-quality evidence**	Not addressed
16: In IBD patients with symptomatic acute splanchnic vein thrombosis (portal, mesenteric and/or splenic vein thrombosis), we recommend anticoagulant therapy over no anticoagulant therapy. **GRADE: Strong recommendation, low-quality evidence**	Consistent
16a–part 1: For patients with clinically inactive IBD who are diagnosed with symptomatic acute splanchnic vein thrombosis in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. **GRADE: Strong recommendation, low-quality evidence**	Consistent
16a–part 2: For IBD patients who are diagnosed with symptomatic acute splanchnic vein thrombosis in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy. **GRADE: Weak recommendation, low-quality evidence**	Consistent
16b: For IBD patients who are diagnosed with symptomatic acute splanchnic vein thrombosis while in clinical remission and in the absence of another provoking factor, we suggest indefinite anticoagulant therapy with periodic review of this decision. **GRADE: Weak recommendation, low-quality evidence**	Consistent

Table 1. Continued

Background statements	Consistency with ACCP[2–6]
16c: In IBD patients with incidentally detected splanchnic vein thrombosis that is not associated with symptoms, we suggest no anticoagulant therapy over anticoagulant therapy. **GRADE: Weak recommendation, very low-quality evidence**	Consistent
17a: For pediatric patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. **GRADE: Strong recommendation, very low-quality evidence**	Consistent
17b: For pediatric IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy. **GRADE: Weak recommendation, very low-quality evidence**	Not addressed

risk factor for VTE in the ACCP guidelines.[2,3] The risk of VTE during hospitalization for IBD flare is nearly 3-fold higher than that for general cancer patients (13/1000 person-years) and half that for cancer patients, who have highest risk for VTE (ie, metastatic cancer or receiving chemotherapy, 68/1000 person-years).[25]

Recommendations for Prevention of Venous Thromboembolism

Statement 4: For IBD patients who are hospitalized with moderate−severe IBD flares without severe bleeding, we recommend anticoagulant thromboprophylaxis with LMWH, low-dose unfractionated heparin, or fondaparinux over no prophylaxis. *GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly 92%; agree with minor reservations 8%.* Several population- and hospital-based studies have shown that hospitalized IBD patients are at a 1.5- to 2-fold increased risk for VTE compared with inpatients without IBD.[10,26–30] In addition, data suggest that, among hospitalized IBD patients, the rate of asymptomatic VTE was 3-fold higher than symptomatic VTE (13% vs 4%).[31] In IBD patients, this increased risk of VTE is associated with a 2.5-fold higher risk of in-hospital mortality compared with IBD patients without VTE.[26]

Although IBD is not listed as a risk factor for VTE in the current ACCP guidelines,[3] the absolute risk of VTE is similar to other conditions, such as respiratory failure,[28] which is listed as a risk factor. This recommendation is based on evidence that IBD is a high-risk condition for in-hospital VTE, observational data that anticoagulant prophylaxis does not increase bleeding in patients with IBD (refer to Statement 6),[32] and strong evidence that anticoagulant prophylaxis markedly reduces VTE in surgical and medical patients.[3] Although LMWH is most commonly used, low-dose unfractionated heparin or fondaparinux are acceptable alternatives, depending on availability at local hospital formularies.

Our recommendation for IBD patients are consistent with guidelines for the general management of UC from the American College of Gastroenterology,[33] the British Society of Gastroenterology,[34] the Canadian Association of Gastroenterology,[35] and the European Crohn's and Colitis Organisation.[36,37]

Statement 5: For IBD patients who are hospitalized for indications unrelated to their IBD, including those in clinical remission, we suggest anticoagulant thromboprophylaxis. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 62%; agree with minor reservations 38%.* The UK cohort study showed that hospitalized IBD patients, even those in clinical remission, had a higher risk of VTE compared with patients without IBD (all patients 2.1; 95% CI: 1.4−3.2,

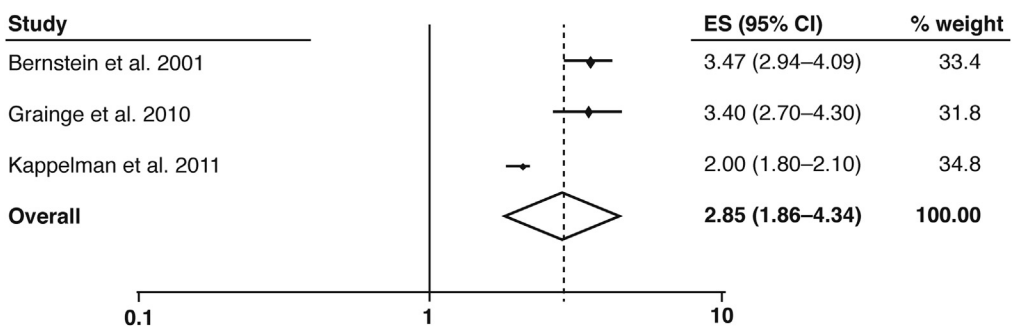

Figure 2. Meta-analysis of population-based studies estimating the risk of VTE in IBD patients.

patients in remission 1.7; 95% CI: 1.1−2.9).[10] The absolute risk of VTE among hospitalized IBD patients in remission (20.9/1000 person-years) was 3-fold higher than among nonhospitalized patients with flare (6.4/1000 person-years) and >20-fold higher than nonhospitalized patients in remission (0.9/1000 person-years).[10] Remission was defined as no requirement for corticosteroids rather than by a validated disease activity scale. It is unclear why hospitalized patients in remission have a higher risk of VTE compared with non-IBD patients during hospitalization. This might be due to comorbid conditions, subclinical active disease, or the presence of other provoking risk factors, such as immobility, trauma, or surgery; however, these clinical factors were not analyzed in the UK study.

Because anticoagulant thromboprophylaxis appears to be safe in hospitalized IBD patients,[32] we recommend prophylaxis for IBD patients during hospitalization regardless of indication for admission, as per the ACCP recommendation for acutely ill hospitalized medical patients at increased risk of thrombosis.[3] The consensus group considered whether, in patients with clinically inactive IBD, anticoagulant prophylaxis should be offered only to patients who were expected to remain in hospital for at least 3 days, which is the duration of reduced mobility that is considered a risk factor for VTE.[3] We do not include a minimum duration of hospitalization in the recommendation because the reason for admission will often be a risk factor for VTE; IBD is an independent risk factor for VTE; and it is often difficult to predict length of stay at the time of admission. However, anticoagulant thromboprophylaxis might not be necessary in individuals with planned admissions of <48 hours for the sole indication of diagnostic testing or nonsurgical procedures.

Statement 6: For hospitalized IBD patients with nonsevere gastrointestinal bleeding related to their disease, we suggest anticoagulant thromboprophylaxis. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 92%; agree with minor reservations 8%.* Although gastrointestinal bleeding is usually a contraindication for anticoagulation, the majority of gastroenterologists in North American surveys only considered it contraindicated in IBD patients if there was hemodynamic compromise.[12,13] This view is supported by a retrospective study that showed that, among 196 hospitalized IBD patients who initially presented with rectal bleeding and received anticoagulant prophylaxis, only 6% continued to have minor bleeding and none developed major bleeding.[32] There are additional safety data from a series of clinical trials in which therapeutic-dose heparin was administered as primary therapy for UC (and CD in one study).[38–42] Using data reported in a meta-analysis of 8 clinical trials,[40] we calculated the incidence of bleeding and found that the difference between those who did and did not receive heparin was not statistically significant (9.1 vs 4.2 per 100 person-years; $P = .55$). A controlled clinical trial that was not included in the meta-analysis reported no bleeding complications in 61 patients treated with heparin.[43] These 9 studies suggest that there is a low absolute risk of increased bleeding in patients with active IBD (mostly UC) who are treated with therapeutic-dose heparin, but do not exclude that heparin might still increase such bleeding.

Because hospitalized patients with IBD are a high-risk group for VTE, and there is little evidence that heparin is associated with an increase in bleeding in these patients,[38–40] we suggest anticoagulant prophylaxis on admission for hospitalized IBD patients with nonsevere gastrointestinal bleeding. This recommendation differs from the strong ACCP recommendation against use of pharmacologic prophylaxis in acutely ill hospitalized medical patients who are bleeding.[3] If there appears to be an increase in bleeding in response to anticoagulant prophylaxis, this treatment should be stopped and mechanical methods of prophylaxis (preferably intermittent pneumatic compression [IPC]) used instead (see Statement 7a).

Statement 7a: For hospitalized IBD patients who have severe IBD-related gastrointestinal bleeding, we suggest mechanical thromboprophylaxis (preferably IPC) over no prophylaxis. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 62%; agree with minor reservations 38%.*

Statement 7b: If bleeding becomes no longer severe, we suggest anticoagulant thromboprophylaxis be substituted for mechanical thromboprophylaxis. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 100%.* Anticoagulants are expected to increase bleeding in IBD patients who are already bleeding severely. Consistent with the ACCP guidelines, we suggest that mechanical methods of prophylaxis, preferably with IPC, should be used in these patients in preference to no prophylaxis, graduated compression stockings, or anticoagulant prophylaxis. This recommendation is based primarily on the findings of the CLOTS (Clots in Legs or Stockings After Stroke) 1 and CLOTS 3 studies, which were controlled trials in patients with acute ischemic stroke. CLOTS 1 found that thigh-level graduated compression stockings did not reduce DVT (odds ratio [OR] = 0.95; 95% CI: 0.73−1.29), and CLOTS 3 found that IPC was effective (OR = 0.65; 95% CI: 0.51−0.84).[44]

Because anticoagulant prophylaxis appears to be more effective for preventing VTE than IPC, and IPC is harder to use properly and curtails patient mobility, we suggest switching to an anticoagulant once bleeding is no longer severe. This recommendation is consistent with preferences elicited in surveys of American and Canadian gastroenterologists,[12,13] and with ACCP recommendations for patients at high risk for VTE with severe bleeding.[3]

Statement 8: For IBD patients who have undergone major abdominal-pelvic or general surgery, we recommend anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. *GRADE: Strong recommendation, moderate-quality evidence. Vote: agree strongly 100%.* Surgical IBD patients, particularly those with UC, are at increased risk for VTE compared with surgical patients without IBD.[45] Among all surgical patients, IBD was associated with a 2-fold increase in risk for VTE (OR = 2.03; 95% CI: 1.52−2.70) in the

American College of Surgeons National Surgical Quality Improvement Program.[46] In a single-center cohort study, among patients who underwent colorectal surgery, the risk of VTE was 7-fold higher in IBD patients compared with cancer patients.[45]

In the large National Surgical Quality Improvement Program cohort study, the observed risk of postoperative VTE was 3.3% in UC and 1.4% in CD patients.[47] Based on ACCP guidelines for risk stratification, if these rates are adjusted for likely VTE prophylaxis usage, the risk of VTE in the absence of prophylaxis is estimated to correspond to a high 6% risk in UC patients and to a moderate 3% risk in CD patients.[4] CD and UC patients who undergo major surgery also satisfy criteria for at least moderate risk using the Caprini Risk Assessment Model.[4,48,49] In a retrospective review of 570 IBD patients who underwent major abdominal surgery, there was no statistically significant difference in risk of major bleeding between those who did and did not receive anticoagulant VTE prophylaxis (0.4% vs 0%; $P = .96$).[32]

As summarized in the ACCP guidelines, in patients who have major nonorthopedic surgery, there is moderate quality evidence for the efficacy of low-dose unfractionated heparin and LMWH over no prophylaxis, but with an increased risk of bleeding.[4]

Therefore, consistent with the ACCP guidelines, we recommend anticoagulant VTE prophylaxis over no prophylaxis for IBD patients who have undergone major abdominal-pelvic or general surgery.[4] The ACCP guidelines also suggest the use of mechanical prophylaxis in addition to anticoagulant thromboprophylaxis for high-risk patients. Patients with UC,[4] and all IBD patients with additional risk factors, such as malignancy, personal or family history of VTE, or hereditary and acquired thrombophilia, are expected to be in this high-risk category and can therefore benefit from additional use of mechanical prophylaxis.[4]

IBD patients should receive anticoagulant prophylaxis throughout their postoperative hospital stay. However, the risk for VTE persists after discharge. In a retrospective cohort population-based study, 17% of postoperative VTEs in UC patients occurred after hospital discharge.[50] There is, however, insufficient evidence to recommend routine post-discharge anticoagulation in UC patients. IBD patients who undergo major surgery for cancer and those with a history of VTE should, however, receive anticoagulant prophylaxis for 4 weeks after surgery, as recommended in ACCP guidelines.[4]

Statement 9: In outpatients presenting with an IBD flare who have not had a previous VTE, we recommend against anticoagulant thromboprophylaxis. *GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly 92%; agree with minor reservations 8%.* Although outpatient flares of IBD increase the risk of thrombosis about 16-fold, the absolute risk is low (0.16% during a 3-month period) and about one sixth of that during an inpatient flare.[10] Assuming the efficacy of thromboprophylaxis in IBD patients is similar to that seen in hospitalized medical patients, the risk of PE and DVT would be decreased by close to two thirds with anticoagulant prophylaxis.[51] In a decision analysis using Markov simulations, it was estimated that 32 IBD patients would have to receive anticoagulant prophylaxis during every IBD flare of their life to prevent one episode of VTE.[52] At a cost of $1,267,450 for every quality-adjusted life year (QALY) gained, such an intervention was not cost effective.[52]

Therefore, we recommend against the use of anticoagulant thromboprophylaxis during an outpatient IBD flare in those with no previous VTE. This recommendation is consistent with the ACCP guideline not to use anticoagulant prophylaxis for outpatients with cancer who have no additional risk factors for VTE, a group that is estimated to have a risk of VTE that is twice that of outpatients with an IBD flare.[3] Recommendations about use of anticoagulant prophylaxis during an outpatient IBD flare in those with a previous VTE are presented in Statement 10.

Statement 10: For IBD outpatients with a previous VTE who are no longer on anticoagulation, we suggest anticoagulant thromboprophylaxis during moderate−severe IBD flares unless all previous episodes of VTE occurred after major surgery. *GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly 31%; agree with minor reservations 61%; agree with major reservations 8%.* This recommendation is based on the working group's assessment that IBD flares serve as an important reversible provoking risk factor for VTE (refer to Statement 2[10]); patients with IBD have an increased risk of recurrent VTE (refer to Statement 14[53]); anticoagulant prophylaxis will reduce recurrent VTE by close to two thirds (refer to Statements 8 and 14[2,4]); and anticoagulant prophylaxis is unlikely to result in a substantial increase in bleeding in IBD (refer to Statement 6[32,51]).

Consistent with this recommendation, a decision analysis that compared administration of once-daily subcutaneous LMWH during outpatient flares with no anticoagulation found that, during a lifetime, this approach was associated with a 0.49 gain in QALYs at a cost of $39,255/QALY.[54] The working group acknowledges that there are organizational and cost barriers to implementing this recommendation and that, in addition, patients might object to daily injections of LMWH. In the absence of strong supporting evidence of benefit, it is reasonable that organizational considerations, cost, and patient preference should influence this treatment decision.

The working group does not recommend anticoagulant thromboprophylaxis during IBD flares in outpatients who have had prior VTE provoked only by surgery because this subgroup of patients has a very low risk of recurrence.[55] Compared with having surgery, an IBD flare is thought to be a modest provoking factor. This exception does not apply to nonsurgical IBD inpatients, who are addressed in Statements 5 and 6.

Statement 11: For pediatric IBD patients (younger than 18 years of age) without a previous VTE who are admitted for an IBD flare, we suggest against anticoagulant thromboprophylaxis. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 69%; agree with minor reservations 16%; agree with major reservations 15%.* The absolute

incidence of VTE was substantially lower in IBD patients 20 years old or younger (8.9/10,000 person-years) than in adults 41 to 60 years (24.1/10,000 person-years) and those older than 60 years (54.6/10,000 person-years).[11] Compared with pediatric patients without IBD, hospitalized children and adolescents with IBD had a >2-fold increased risk of VTE (relative risk = 2.36; 95% CI: 2.15−2.58), although the risk was lower in nonsurgical IBD patients (relative risk = 1.22; 95% CI: 1.08−1.36).[56] Although hospitalized pediatric IBD patients have an increased relative risk of VTE compared with children without IBD,[11,26,56] the absolute risk of VTE is much lower than that in adults with IBD.[11,26]

Given the lower risk of VTE and the discomfort of subcutaneous injections, we suggest against use of anticoagulant thromboprophylaxis for pediatric IBD patients hospitalized with a flare. However, we suggest that anticoagulant prophylaxis be used in hospitalized IBD patients with a history of lower-extremity DVT or pulmonary embolism, and in older overweight adolescents who have surgery (refer to Statement 4) because they might have a risk of VTE that is more similar to the adult IBD population.

Statement 12: For pregnant women with IBD who have undergone cesarean section, we suggest anticoagulant thromboprophylaxis during hospitalization over no prophylaxis. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 84%; agree with minor reservations 8%; agree with major reservations 8%.* There are several lines of evidence to suggest that pregnant women with IBD are at increased risk of VTE compared with pregnant women without IBD. In a UK retrospective population-based cohort study, women with IBD had an adjusted relative incidence of VTE of 3.50 (95% CI: 1.12−10.9) in the antepartum period and 4.07 (95% CI: 1.73−9.57) in the 12-week postpartum period compared with women without IBD.[57] The corresponding absolute risks in the antepartum and postpartum periods were 2.9/1000 person-years and 15.1/1000 person-years, respectively. Another European population-based retrospective cohort study also found an elevated risk of VTE during pregnancy among women with UC (OR = 3.78; 95% CI: 1.52−9.38) or CD (OR = 1.26; 95% CI: 0.35−4.53).[58] When the postpartum and antepartum periods were combined, the OR was 2.31 (95% CI: 1.09−4.89). The risks were particularly high among pregnant women with UC during flare (OR 25.0; 95% CI: 2.49−250) compared with pregnant women without IBD.[58]

A third retrospective, nationwide US study found that IBD was associated with a >6-fold higher risk of VTE during hospitalizations for delivery (UC: OR = 8.4; 95% CI: 3.7−19.2, CD: OR = 6.1; 95% CI: 2.9−12.9).[59] In addition, women with IBD are more likely to undergo cesarean section (close to 50% in the United States), which is an independent risk factor for VTE (OR = 1.7; 95% CI: 1.5−1.9).[58,59]

IBD is not explicitly considered a risk factor for postpartum VTE in the ACCP guidelines for VTE in pregnancy. However, because CD and UC are estimated to increase postpartum VTE at least 6-fold, each is considered a major risk factor for VTE after Cesarean section, as per criteria outlined in the ACCP guidelines.[6] Therefore, we suggest that women with IBD who have Cesarean section should receive anticoagulant thromboprophylaxis during the hospitalized postpartum period over no prophylaxis unless postpartum hemorrhage has occurred. In addition, if there is a history of VTE, we suggest prophylaxis for up to 6 weeks after delivery.[6]

Treatment of Venous Thromboembolism

Statement 13: In patients with VTE, co-existing IBD is not an indication for testing for hereditary or acquired hypercoagulable states. *GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly 77%; agree with minor reservations 23%.* Inherited thrombophilia does not appear be more common in the adult or pediatric IBD population than the general population.[60,61] Two meta-analyses showed that there was no statistically significant association between IBD and Factor V Leiden.[62,63] In addition, many studies have shown no association between IBD and Prothrombin G20210.[60,61,64–68] Likewise, the vast majority of studies have not shown an association between IBD and MTHFR and Factor XIII val34leu.[60,61,65–75]

Several studies have demonstrated an increased prevalence of antiphospholipid antibodies among IBD patients compared with healthy controls.[71,76–79] A decrease in the natural anticoagulants, protein C, protein S, and antithrombin activity have also been reported in several studies and are postulated to be a consequence of disease activity.[71,79–81]

Similar to other patients who have VTE associated with a provoking factor, the prevalence of thrombophilic abnormalities is expected to be lower in patients with VTE and IBD than in patients with unprovoked VTE. The presence of hereditary or acquired thrombophilias does not usually influence treatment of VTE (ie, type or duration of anticoagulation), including in patients with IBD.[2,82,83] Consequently, we do not consider that thrombophilia testing is helpful in the anticoagulant management of patients with IBD and VTE, including in individuals with unprovoked VTE while their IBD is in clinical remission.

Statement 14: For IBD patients who are diagnosed with their first episode of VTE while in clinical remission, and in the absence of another provoking factor, we suggest indefinite anticoagulant therapy with periodic review of this decision. *GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly 77%; agree with minor reservations 23%.* A European multicenter cohort study of 86 IBD patients with a first unprovoked VTE showed that the 5-year risk of recurrence was 33% (95% CI: 22%−45%) after discontinuing anticoagulant therapy, and that IBD was associated with a 2.5-fold (95% CI: 1.4−4.2; adjusted for confounding factors) risk of recurrence compared with non-IBD patients with a first unprovoked VTE.[53] These data suggest that IBD is a continuing risk factor for recurrent

VTE and, therefore, support indefinite anticoagulant therapy in patients with IBD who have VTE without an additional reversible provoking factor, such as recent surgery. However, the benefits of indefinite therapy must be weighed against the risks of bleeding. A decision analysis estimated that lifelong anticoagulation after an initial episode of otherwise unprovoked VTE in patients with IBD resulted in a 0.47 gain in QALYs and lower costs compared with anticoagulation limited to only 6 months.[54]

In accordance with the ACCP guidelines,[2] we suggest indefinite therapy for IBD patients who are diagnosed with their first episode of unprovoked proximal DVT or PE when in clinical remission, provided they do not have a high risk of bleeding and are not strongly opposed to indefinite therapy. An exception to this suggestion is the occurrence of isolated distal DVT (ie, DVT of the calf veins without involvement of the popliteal or more proximal veins). Because these have half the risk of recurrence of proximal DVT, we concur with the ACCP guidelines that if patients are diagnosed with *a first unprovoked isolated distal DVT,* they should be treated for 3 months and not receive indefinite anticoagulant therapy.[2,53] The need for anticoagulation should be reviewed at least annually, with consideration of factors such as changes in the patient's IBD disease state, risk of bleeding, patient preferences, and emerging research in the area.

Statement 15a: For patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. *GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly 62%; agree with minor reservations 38%.*

Statement 15b: For IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy. *GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly 62%; agree with minor reservations 38%.* Nearly one quarter of IBD patients have another provoking factor, such as recent surgery, trauma, oral contraceptive use, or presence of an indwelling catheter, when VTE is diagnosed.[19,53] Given strong evidence that patients with VTE provoked by a reversible risk factor have a much lower risk of recurrence than patients without a reversible risk factor,[2,55] the working group believes that patients who develop VTE when their IBD is in remission and in the presence of a reversible provoking factor need only be treated for 3 months, similar to patients without IBD who have VTE provoked by a reversible risk factor.[2]

In addition, the working group considers IBD disease flare to be a reversible provoking factor. As noted in Statement 2, a moderate–severe disease flare is a strong risk factor for development of a first VTE. Although we consider it a reversible provoking factor, an IBD flare can last from weeks to years and the risk of recurrent VTE is expected to be higher in patients with IBD in remission than in other patients with a reversible provoking risk factor.[10] For these reasons, we suggest that anticoagulant therapy be continued until 3 months after the IBD flare has resolved over just treating patients for 3 months or treating patients indefinitely. For the purposes of discontinuing anticoagulant therapy 3 months after remission of IBD, the treating physician should use clinical assessments to decide when remission has been achieved.[2]

Statement 16: In IBD patients with symptomatic acute splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thrombosis), we recommend anticoagulant therapy over no anticoagulant therapy. *GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly 85%; agree with minor reservations 15%.*

Statement 16a—part 1: For patients with clinically inactive IBD who are diagnosed with symptomatic acute splanchnic vein thrombosis in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. *GRADE: Strong recommendation, low-quality evidence. Vote: agree strongly 92%; agree with minor reservations 8%.*

Statement 16a—part 2: For IBD patients who are diagnosed with symptomatic acute splanchnic vein thrombosis in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 85%; agree with minor reservations 15%.*

Statement 16b: For IBD patients who are diagnosed with symptomatic acute splanchnic vein thrombosis when in clinical remission and in the absence of another provoking factor, we suggest indefinite anticoagulant therapy with periodic review of this decision. *GRADE: Weak recommendation, low-quality evidence. Vote: agree strongly 85%; agree with minor reservations 15%.*

Statement 16c: In IBD patients with incidentally detected splanchnic vein thrombosis that is not associated with symptoms, we suggest no anticoagulant therapy over anticoagulant therapy. *GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly 62%; agree with minor reservations 38%.* Data on the burden of intra-abdominal VTE in IBD patients are available from retrospective cohort studies.[19,84–86] A survey of 2784 IBD outpatients found splanchnic vein thrombosis in 0.3% of patients (0.3/1000 person-years).[19] Among hospitalized UC patients, the incidence of clinically detected splanchnic vein thrombosis was 3.3% (49% of VTEs) in those who underwent colectomy and 0.3% in those who did not.[50] Another study showed a similar rate of 4.8% in IBD patients who underwent colectomy.[84] In other IBD clinic-based studies, the lifetime incidence of splanchnic vein thrombosis was 1.1%

to 1.3%, two thirds of which occurred in the perioperative setting.[85,86] Therefore, surgery is an important provoking factor for splanchnic vein thrombosis in the IBD population. In addition, as described in Statement 2, disease flare increases the risk for VTE and is expected to increase the risk for splanchnic vein thrombosis. One quarter of patients with nonmalignant and noncirrhotic splanchnic vein thrombosis have a myeloproliferative neoplasm, with the splanchnic vein thrombosis usually diagnosed first. Therefore, myeloproliferative neoplasms should be considered in IBD patients with splanchnic vein thrombosis, particularly if there is no additional provoking factor (eg, recent surgery or disease flare). Testing for the JAK2V617F mutation, which is present in a majority of patients, is helpful for identifying this disorder.[87]

Because there is evidence that anticoagulation is not associated with an important increased risk of major bleeding in the IBD population,[40] and in the absence of data specific to the management of splanchnic vein thrombosis in IBD, our recommendations for this population mirror those for proximal DVT and PE in IBD patients. Similar to the treatment of VTE at other sites, we recommend anticoagulant treatment for symptomatic splanchnic vein thrombosis, and suggest anticoagulation for 1 month after resolution of the provoking factor or 3 months after a disease flare. For IBD patients with unprovoked splanchnic vein thrombosis, we suggest indefinite anticoagulation with periodic review of this decision.[53] Our recommendations are in agreement with the ACCP guidelines for the treatment of splanchnic vein thrombosis.[2]

We suggest not treating most patients with asymptomatic splanchnic vein thrombosis. However, anticoagulant therapy might be favored in patients with acute, extensive thrombosis; progression of thrombosis on a follow-up imaging study; and those receiving ongoing cancer chemotherapy.[2] In addition, it might be difficult to distinguish symptoms of splanchnic vein thrombosis from those of IBD or related surgery.[84] If it is unclear whether gastrointestinal symptoms are related to splanchnic vein thrombosis or to the underlying IBD, we suggest erring on the side of treatment with anticoagulation.

Statement 17a: For pediatric patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. *GRADE: Strong recommendation, very low-quality evidence. Vote: agree strongly 92%; agree with minor reservations 8%.*

Statement 17b: For pediatric IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy. *GRADE: Weak recommendation, very low-quality evidence. Vote: agree strongly 85%; agree with minor reservations 15%.* Low-quality data from case series suggests that the average risk of recurrent VTE in pediatric IBD patients is about 10% over follow-up periods that varied from 1 month to several years.[88] The guideline committee believes that there are insufficient data in the pediatric IBD population to warrant deviation from recommendations for the general pediatric population. Therefore, in pediatric IBD patients with VTE provoked by an unrelated clinical risk factor that has resolved, we recommend anticoagulant therapy for 3 months, in accordance with the ACCP guidelines for the treatment of children with VTE.[5] If the unrelated provoking factor is ongoing, we recommend continuing anticoagulant therapy for at least 3 months and until that risk factor has resolved for 1 month. For pediatric IBD patients who develop VTE during a disease flare, our recommendation to treat with anticoagulant therapy for 3 months after achieving clinical remission mirrors our recommendation for the adult IBD population (Statement 15a).

Summary

These consensus statements identify when and how the 9th ACCP guidelines on antithrombotic therapy and prevention of thrombosis should be applied to patients with IBD, and how patients with IBD should be managed when those guidelines are not appropriate or have not addressed issues that are specific to IBD patients. The strength of our recommendations is based on an overall assessment of the risk−benefit profile of alternative management strategies, quality of evidence, expected patient preferences, and economic considerations. The working group unanimously agreed on all consensus statements, and several garnered strong recommendations.

For the prevention of VTE, strong recommendations are made for anticoagulant thromboprophylaxis over no prophylaxis for patients with IBD who are hospitalized with moderate−severe IBD flares without severe bleeding; for anticoagulant thromboprophylaxis over no prophylaxis for inpatients with IBD who have undergone major abdominal-pelvic or general surgery; and against anticoagulant thromboprophylaxis in outpatients with an IBD flare if they have not had a previous VTE.

For the treatment of VTE, strong recommendations are made for a minimum of 3 months of anticoagulant therapy for adult and pediatric IBD patients with a symptomatic DVT, PE, or splanchnic vein thrombosis. We also strongly recommend that if anticoagulant therapy is being stopped in patients with a reversible provoking factor, it should not be stopped until the risk factor has resolved for at least 1 month.

Because there are no clinical trials addressing VTE prophylaxis and treatment specifically in patients with IBD, none of the evidence was rated as high quality. When interpreting the available evidence, we generally gave strong recommendations when we were confident that following the recommendation would benefit patients. These strong recommendations were usually based on strong observational data, such as in our recommendation that IBD is not an indication for hereditary hypercoagulable states, or strong clinical trial data that could be extrapolated

to patients with IBD, such as in our recommendation for use of prophylaxis in IBD patients who were hospitalized with moderate to severe flares. In the absence of forthcoming clinical trials in the IBD population, these recommendations will provide clinicians with an evidence-based approach to the challenging issues in the management of VTE among those with IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.01.042.

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Supplementary Table 1. Search Strategies Used for Medline and EMBASE

EMBASE	Medline
1. enteritis/ or necrotizing enteritis/	1. inflammatory bowel diseases/ or colitis, ulcerative/ or crohn disease/
2. Crohn disease/	2. ("inflammatory bowel disease*" or (Crohn's or Crohn) or "ulcerative colitis").tw.
3. ulcerative colitis/	3. 1 or 2
4. ("inflammatory bowel disease*" or (Crohn's or Crohn) or "ulcerative colitis").tw.	4. Venous Thromboembolism/ or Pulmonary Embolism/ or Thromboembolism/
5. or/1−4	5. Thrombophilia/
6. lung embolism/ or thromboembolism/ or venous thromboembolism/ or deep vein thrombosis/ or thrombosis/ or vein thrombosis/	6. (venous thromboembolism or thromboembolism or venous thrombosis or venous thromboembolic disease or deep venous thrombosis or pulmonary embolism or thrombosis or vein thrombosis or hypercoagulability or hypercoagulable state or thrombophili*).tw.
7. hypercoagulability/	7. or/4−6
8. thrombophilia/	8. Anticoagulants/
9. (venous thromboembolism or thromboembolism or venous thrombosis or venous thromboembolic disease or deep venous thrombosis or pulmonary embolism or thrombosis or vein thrombosis or hypercoagulability or hypercoagulable state or thrombophili*).tw.	9. anticoagula*.tw.
10. or/6−9	10. Vitamin K/ai [Antagonists & Inhibitors]
11. anticoagulant agent/ or anticoagulation/	11. Vitamin K antagonist*.tw.
12. anticoagula*.tw.	12. Thrombolytic Therapy/ or Mechanical Thrombolysis/
13. antivitamin K/	13. (thrombolysis or thrombolytic or mechanical thromboprophylaxis).tw.
14. Vitamin K antagonist*.tw.	14. Intermittent Pneumatic Compression Devices/
15. blood clot lysis/	15. intermittent pneumatic compression.tw.
16. fibrinolytic therapy/	16. Stockings, Compression/
17. (thrombolysis or thrombolytic or mechanical thromboprophylaxis).tw.	17. graduated compression stockings.tw.
18. intermittent pneumatic compression device/	18. Warfarin/
19. intermittent pneumatic compression.tw.	19. (Warfarin* or Coumarin or Athrombine-K or Brumolin or Coumadin or Coumafen or Coumafene or Coumaphene or Coumarins or Coumefene or Dethmor or Dethnel or Dicusat or Kumader or Kumadu or Kumatox or Kypfarin or Latka or Mar-frin or Maveran or Panwarfin or Place-Pax or Prothromadin or Solfarin or Tox-Hid or Vampirinip or Warfarat or Zoocoumarin).tw.
20. compression garment/	20. Heparin/ or Heparin, Low-Molecular-Weight/
21. graduated compression stockings.tw.	21. (Heparin* or Bemiparin or Certoparin or Fluxum or Parnaparin or Reviparin or Sandoparin or Ardeparin or Arteven or Bemiparin or Certoparin or Clexane or Clivarin or Clivarine or Dalteparin or Eparina or Fluxum or Fragmin or Fraxiparin or Hepathrom or Lipo-hepin or Liquaemin or Liquemin or Multiparin or Nadroparin or Nadroparine or Novoheparin or Octaparin or Pabyrin or Parnaparin or Parvoparin or Pularin or Reviparin or Sandoparin or Semuloparin or Subeparin or Sublingula or Thromboliquine or Tinzaparin or Triofiban or Vetren or Vitrum).tw.
22. warfarin/	22. Nadroparin/
23. (Warfarin* or Coumarin or Athrombine-K or Brumolin or Coumadin or Coumafen or Coumafene or Coumaphene or Coumarins or Coumefene or Dethmor or Dethnel or Dicusat or Kumader or Kumadu or Kumatox or Kypfarin or Latka or Mar-frin or Maveran or Panwarfin or Place-Pax or Prothromadin or Solfarin or Tox-Hid or Vampirinip or Warfarat or Zoocoumarin).tw.	23. dabigatran.tw.
24. heparin/ or low molecular weight heparin/	24. (Rivaroxaban or BAY59-7939 or UNII-9NDF7JZ4M3 or Xarelto).tw.
25. (Heparin* or Bemiparin or Certoparin or Fluxum or Parnaparin or Reviparin or Sandoparin or Ardeparin or Arteven or Bemiparin or Certoparin or Clexane or Clivarin or Clivarine or Dalteparin or Eparina or Fluxum or Fragmin or Fraxiparin or Hepathrom or Lipo-hepin or Liquaemin or Liquemin or Multiparin or Nadroparin or Nadroparine or Novoheparin or Octaparin or Pabyrin or Parnaparin or Parvoparin or Pularin or Reviparin or Sandoparin or Semuloparin or Subeparin or Sublingula or Thromboliquine or Tinzaparin or Triofiban or Vetren or Vitrum).tw.	25. (Apixaban or BMS-562247-01 or Eliquis or UNII-3Z9Y7UWC1J).tw.
26. dabigatran/	26. (Fondaparinux or HSDB 7845 or Org-31540 or PENTA or SR 90107 or UNII-J177FOW5JL).tw.
27. dabigatran.tw.	27. Enoxaparin/
28. rivaroxaban/	28. (Enoxaparin or Clexane or Klexane or Lovenox or UNII-8NZ41MIK1O).tw.
29. (Rivaroxaban or BAY59-7939 or UNII-9NDF7JZ4M3 or Xarelto).tw.	29. Dalteparin/
30. apixaban/	30. (Dalteparin or FR-860 or Fragmin or Fragmine or Kabi-2165 or Tedelparin).tw.
31. (Apixaban or BMS-562247-01 or Eliquis or UNII-3Z9Y7UWC1J).tw.	31. (Tinzaparin or Innohep or UNII-7UQ7X4Y489).tw.
32. fondaparinux/	32. or/8−31
33. (Fondaparinux or HSDB 7845 or Org-31540 or PENTA or SR 90107 or UNII-J177FOW5JL).tw.	33. 3 and (7 or 32)
34. enoxaparin/	34. exp animals/ not humans.sh.
35. (Enoxaparin or Clexane or Klexane or Lovenox or UNII-8NZ41MIK1O).tw.	35. 33 not 34

Supplementary Table 1. Continued

EMBASE	Medline
36. dalteparin/	36. (letter or news).pt.
37. (Dalteparin or FR-860 or Fragmin or Fragmine or Kabi-2165 or Tedelparin).tw.	37. exp Case Reports/
38. tinzaparin/	38. 35 not (36 or 37)
39. (Tinzaparin or Innohep or UNII-7UQ7X4Y489).tw.	39. limit 38 to English language
40. bemiparin/	
41. certoparin/	
42. nadroparin/	
43. parnaparin/	
44. reviparin/	
45. or/11-44	
46. 5 and (10 or 45)	
47. (animal$ not human$).sh,hw.	
48. 46 not 47	
49. (letter or note).pt.	
50. case report/	
51. 48 not (49 or 50)	
52. limit 51 to English language	

Supplementary Table 2. ACCP Recommendations Referenced in CAG Statements

CAG statement no.	ACCP recommendation	ACCP guideline
4: For IBD patients who are hospitalized with moderate−severe IBD flares without severe bleeding, we recommend anticoagulant thromboprophylaxis with LMWH, LDUFH, or fondaparinux over no prophylaxis. 5: For IBD patients who are hospitalized for indications unrelated to their IBD, including those in clinical remission, we suggest anticoagulant thromboprophylaxis. 6: For hospitalized IBD patients with nonsevere gastrointestinal bleeding related to their disease, we suggest anticoagulant thromboprophylaxis. 7a: For hospitalized IBD patients who have severe IBD-related gastrointestinal bleeding, we suggest mechanical thromboprophylaxis (preferably IPC) over no prophylaxis. 7b: If bleeding becomes no longer severe, we suggest anticoagulant thromboprophylaxis be substituted for mechanical thromboprophylaxis.	2.3: For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with LMWH, LDUFH bid, LDUFH tid, or fondaparinux (grade 1B)	Kahn et al,[3] Prevention in nonsurgical patients[3]
7a: For hospitalized IBD patients who have severe IBD-related gastrointestinal bleeding, we suggest mechanical thromboprophylaxis (preferably IPC) over no prophylaxis. **7b:** If bleeding becomes no longer severe, we suggest anticoagulant thromboprophylaxis be substituted for mechanical thromboprophylaxis.	**2.7.2:** For acutely ill hospitalized medical patients at increased risk of thrombosis who are bleeding or at high risk for major bleeding, we suggest the optimal use of mechanical thromboprophylaxis with graduated compression stockings (grade 2C) or IPC (grade 2C), rather than no mechanical thromboprophylaxis. When bleeding risk decreases, and if VTE risk persists, we suggest that pharmacologic thromboprophylaxis be substituted for mechanical thromboprophylaxis (grade 2B)	Kahn et al,[3] Prevention in nonsurgical patients
8: For IBD patients who have undergone major abdominal-pelvic or general surgery, we recommend anticoagulant thromboprophylaxis during hospitalization over no prophylaxis.	**3.6.3**: For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score, >10; Caprini score, 3−4) who are not at high risk for major bleeding complications, we suggest LMWH (grade 2B), LDUFH (grade 2B) , or mechanical prophylaxis, preferably with IPC (grade 2C), over no prophylaxis **3.6.5**: For general and abdominal-pelvic surgery patients at high risk for VTE (~6.0%; Caprini score, ≥5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (grade 1B) or LDUFH (grade 1B) over no prophylaxis. We suggest that mechanical prophylaxis with elastic stockings or IPC should be added to pharmacologic prophylaxis (grade 2C) **3.6.6:** For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (grade 1B)	Gould et al,[4] Prevention in nonorthopedic surgical patients
9: In outpatients presenting with an IBD flare who have not had a previous VTE, we recommend against anticoagulant thromboprophylaxis.	**4.2.1:** In outpatients with cancer who have no additional risk factors for VTE, we suggest against routine prophylaxis with LMWH or LDUFH (grade 2B) and recommend against the prophylactic use of vitamin K antagonists (grade 1B)	Kahn et al,[3] Prevention in nonsurgical patients
12: For pregnant women with IBD who have undergone Cesarean section, we suggest anticoagulant thromboprophylaxis during hospitalization over no prophylaxis.	**6.2.2:** For women at increased risk of VTE after cesarean section because of the presence of 1 major or at least 2 minor risk factors, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic	Bates et al,[6] Pregnancy

Supplementary Table 2. Continued

CAG statement no.	ACCP recommendation	ACCP guideline
	stockings or IPC) in those with contraindications to anticoagulants while in hospital after delivery rather than no prophylaxis (grade 2B)	
14: For IBD patients who are diagnosed with their first episode of VTE while in clinical remission and in the absence of another provoking factor, we suggest indefinite anticoagulant therapy with periodic review of this decision.	**3.1.4.1:** In patients with a first VTE that is an unprovoked proximal DVT of the leg and who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy over 3 months of therapy (grade 2B) **2.3.1:** In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (grade 2C) **2.3.2:** In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension, we suggest initial anticoagulation over serial imaging of the deep veins (grade 2C) **3.1.4.3:** In patients with a first VTE that is an unprovoked isolated distal DVT of the leg (see note below), we suggest 3 months of anticoagulant therapy over extended therapy in those with a low or moderate bleeding risk (grade 2B) and recommend 3 months of anticoagulant treatment in those with a high bleeding risk (grade 1B) NOTE: Refers to patients in whom a decision has been made to treat with anticoagulant therapy	Kearon et al,[2] Antithrombotic therapy
15a: For patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. **15b:** For IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy.	**3.1.2:** In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over treatment of a shorter period (grade 1B), treatment of a longer time limited period (eg, 6 or 12 months) (grade 1B), and extended therapy if there is a high bleeding risk (grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (grade 2B)	Kearon et al,[2] Antithrombotic therapy
16: In IBD patients with symptomatic acute splanchnic vein thrombosis (portal, mesenteric and/or splenic vein thrombosis), we recommend anticoagulant therapy over no anticoagulant therapy. **16a—part 1:** For patients with clinically inactive IBD who are diagnosed with symptomatic acute splanchnic vein thrombosis in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. **16a—part 2:** For IBD patients who are diagnosed with symptomatic acute splanchnic vein thrombosis in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months, or indefinite anticoagulant therapy. **16b:** For IBD patients who are diagnosed with symptomatic acute splanchnic vein thrombosis while in clinical remission and in the absence of another provoking factor, we suggest indefinite anticoagulant therapy with periodic review of this decision.	**10.1:** In patients with symptomatic splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we recommend anticoagulation over no anticoagulation (grade 1B) **10.2:** In patients with incidentally detected splanchnic vein thrombosis (portal, mesenteric, and/or splenic vein thromboses), we suggest no anticoagulation over anticoagulation (grade 2C)	Kearon et al,[2] Antithrombotic therapy

Supplementary Table 2. Continued

CAG statement no.	ACCP recommendation	ACCP guideline
16c: In IBD patients with incidentally detected splanchnic vein thrombosis that is not associated with symptoms, we suggest no anticoagulant therapy over anticoagulant therapy.		
17a: For pediatric patients with clinically inactive IBD who are diagnosed with their first episode of VTE in the presence of an unrelated reversible provoking factor, we recommend anticoagulant therapy for a minimum of 3 months and until the risk factor has resolved for at least 1 month. **17b:** For pediatric IBD patients who are diagnosed with their first episode of VTE in the presence of active disease, we suggest anticoagulant therapy until the IBD is in remission for 3 months over stopping treatment at 3 months or indefinite anticoagulant therapy.	**2.22.3:** In children with secondary VTE (ie, VTE that has occurred in association with a clinical risk factor) in whom the risk factor has resolved, we suggest anticoagulant therapy be administered for 3 months (grade 2C) as compared with no further therapy. In children who have ongoing, but potentially reversible risk factors, such as active nephrotic syndrome or ongoing asparaginase therapy, we suggest continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved (grade 2C)	Monagle et al,[5] Pediatrics

LDUFH, low-dose unfractionated heparin.

Supplementary Table 3. Disease Activity Index for IBD: Harvey-Bradshaw Index (HBI)[a]

Harvey-Bradshaw Index (HBI)		
1. General well-being (yesterday)	☐ Very well = 0 ☐ Slightly below par = 1 ☐ Poor = 2	☐ Very poor = 3 ☐ Terrible = 4
2. Abdominal pain (yesterday)	☐ None = 0 ☐ Mild = 1	☐ Moderate = 2 ☐ Severe = 3
3. Number of liquid or soft stools per day (yesterday) = _____		
4. Abdominal mass	☐ None = 0 ☐ Dubious = 1	☐ Definite = 2 ☐ Definite and tender = 3
5. Complications (check any that apply; score one per item except for first box)	☐ None = 0 ☐ Arthralgia ☐ Uveitis ☐ Erythema nodosum ☐ Aphthous ulcers	☐ *Pyoderma gangrenosum* ☐ Anal fissure ☐ New fistula ☐ Abscess

Total score = _____
HBI index scoring: remission <5; mild disease 5–7; moderate disease 8–16; severe disease >16

[a]Based on references.[22,23]

Supplementary Table 4. Disease Activity Index for IBD: Modified Mayo Index

Modified Mayo Index	
Stool frequency	Normal = 0 1–2 stools/day more than normal = 1 3–4 stools/day more than normal = 2 >4 stools/day more than normal = 3
Rectal bleeding[a]	None = 0 Visible blood with stool less than half the time = 1 Visible blood with stool half of the time or more = 2 Passing blood alone = 3
Mucosal appearance[b]	Normal or inactive disease = 0 Mild disease (erythema, decreased vascular pattern, mild friability) = 1 Moderate disease (marked erythema, absent vascular pattern, friability, erosions) = 2 Severe disease (spontaneous bleeding, ulceration) = 3
Physician rating of disease	Normal = 0 Mild = 1 Moderate = 2 Severe = 3

Total score = _____
Remission = total score ≤2; response = reduction of ≥3 points.

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[a]A score of 3 for bleeding required patients to have at least 50% of bowel movements accompanied by visible blood and at least one bowel movement with blood alone.
[b]The mucosal appearance at endoscopy is not included in the Partial Mayo Score.