

# Guidelines-Based Use of Thromboprophylaxis

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Thromboprophylaxis with anticoagulants has proven benefits in hospitalized patients. Despite this, venous thromboembolism (VTE) prophylaxis is underused and VTE remains the leading cause of preventable hospital mortality.<sup>1</sup> Medical patients have a particularly high risk; those who develop a deep vein thrombosis (DVT) are significantly less likely to have received prophylaxis prior to the diagnosis of DVT than nonmedical patients. Even within the high-risk setting of the intensive care unit (ICU), medical patients receive thromboprophylaxis only two-thirds as often as non-medical patients.<sup>2</sup>

In this article we summarize the evidence concerning the various prophylaxis options, including current guideline recommendations for VTE prevention in medical and surgical patients. We also discuss strategies for thromboprophylaxis in special populations and potential complications of prophylaxis.

## Efficacy of Prophylaxis in Medical Patients

Several meta-analyses have demonstrated the marked benefits of anticoagulant prophylaxis in medical patients. Dentali et al<sup>3</sup> conducted a meta-analysis of 9 randomized controlled trials enrolling a total of 19,958 at-risk hospitalized medical patients. The selected trials compared standard anticoagu-

lant regimens with no treatment and only included studies with objectively documented and independently adjudicated outcomes. Compared with patients receiving placebo, those receiving thromboprophylaxis had significant reductions in any PE by 57% (95% CI, 0.26-0.71; absolute risk reduction, 0.29%) and fatal pulmonary embolism (PE) by 62% (95% CI, 0.21-0.69; absolute risk reduction, 0.25%), with a nonsignificant reduction in symptomatic DVT (relative risk [RR], 0.47; 95% CI, 0.22-1.00) and a nonsignificant increase in major bleeding (RR, 1.32; 95% CI, 0.73-2.37). The researchers concluded that anticoagulant prophylaxis is effective in preventing symptomatic VTE in medical patients, though the optimal duration of therapy is not yet defined.<sup>3</sup>

Another meta-analysis focusing on subclinical DVT in acutely ill medical patients examined the therapeutic effects of various prophylaxis regimens. Overall, anticoagulant prophylaxis reduced the risk of any asymptomatic DVT (assessed by venogram or ultrasound) by 49% (95% CI, 0.39-0.67) and asymptomatic proximal DVT by 55% (95% CI, 0.31-0.65) compared with placebo (absolute risk reduction, 2.6% and 1.8%, respectively). Although prophylaxis was associated with a 0.5% absolute risk increase in major bleeding, the authors concluded that the benefits of prophylaxis outweighed the risks of bleeding.<sup>4</sup>

**TABLE 1. Anticoagulant Agents for the Prevention of VTE**

|              | Prophylactic Dose  | Warnings/Contraindications/Adverse Reactions   |
|--------------|--|--|
| Warfarin     | 5 to 10 mg daily initially;* adjust dose based on INR; therapeutic INR goal: 2.5 (2-3) | Warning: bleeding risk; requires frequent monitoring; contraindicated in patients for whom hazard of hemorrhage outweighs potential benefit (eg, in pregnant women)  |
| UFH          | 5000 IU every 8-12 hours subcutaneously <sup>†</sup>                                   | Contraindicated in the presence of active bleeding, uncontrolled hypertension, or severe thrombocytopenia; monitor platelet count every 4-7 days for HIT   |
| Dalteparin   | 5000 IU daily subcutaneously   | Warning: spinal/epidural hematoma; monitor for signs and symptoms of neurological impairment. LMWHs should be used with caution in renal impairment; anti-Xa monitoring and dose adjustments may be required. Follow prescribing information for dose adjustments and body weight-based dosing. Most common adverse reactions: bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, and nausea |
| Enoxaparin   | 40 mg daily subcutaneously; reduce to 30 mg daily in renal impairment <sup>‡</sup>     |  |
| Tinzaparin   | 3500 IU daily subcutaneously   |  |
| Fondaparinux | 2.5 mg daily subcutaneously  | Warning: spinal/epidural hematoma; monitor for signs and symptoms of neurological impairment; contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/minute) and in patients < 50 kg   |

NOTE: Adapted from Prescribing Information; Umland<sup>6</sup> and Ansell et al.<sup>5</sup>

**Abbreviations:** aPTT, activated partial thromboplastin time; HIT, heparin-induced thrombocytopenia; INR, International Normalized Ratio; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

\* For elderly and other debilitated/malnourished patients, starting dose should be  $\leq 5$  mg.

<sup>†</sup> Before initiation, perform baseline aPTT and platelet count.

<sup>‡</sup> This is the dose for DVT prophylaxis in abdominal surgery, hip replacement surgery, and medical patients; the dose in knee replacement surgery is 30 mg subcutaneously every 12 hours. Reduce the dose if creatinine clearance  $\leq 30$  mL/minute.

### Anticoagulant Agents in the Prevention of VTE

Currently available anticoagulants for the prevention of VTE include unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), fondaparinux, and warfarin. These agents interrupt thrombus formation, either indirectly (through interaction with antithrombin) or directly (by inhibiting the action of thrombin). Each class of therapy has advantages and limitations. Table 1 lists common anticoagulant options for VTE prophylaxis, along with dosing information and other important information.<sup>5-10</sup>

#### UFH

UFH, which is typically administered by subcutaneous injection, has the longest history as an anticoagulant in the prevention and treatment of VTE. It is an attractive option in patients with severe renal failure or those who may require a procedure in the near future. Although UFH is partially cleared by the kidney, its short half-life can be perceived as a safety advantage in patients with severe renal impairment and an increased risk of bleeding. For most other patients, UFH holds several disadvantages compared with newer therapies, including the need for injections to be administered 3 times a day to be optimally effective, its effect on platelets, and its association with heparin-induced thrombocytopenia (HIT).<sup>1</sup> Given the costs of administration and potential complications, it is not less expensive than LMWHs, and it appears to be less cost-effective.<sup>11</sup>

#### LMWHs

LMWHs have a higher bioavailability and longer half-life than UFH, which translates to reliable anticoagulation levels when given subcutaneously on a weight-based dosing

schedule. Unlike UFH, LMWHs do not require laboratory tests to monitor the intensity of anticoagulation, except in special circumstances.<sup>1</sup> The LMWHs dalteparin, enoxaparin, and tinzaparin are widely used for the prevention and treatment of VTE in the United States.

Two landmark clinical trials demonstrated the efficacy of appropriate thromboprophylaxis with LMWHs in reducing the burden of VTE in acutely ill, hospitalized medical patients. The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial and Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) demonstrated the benefits of enoxaparin and dalteparin, respectively, in reducing the risk of VTE. As shown in Table 2, thromboprophylaxis with these agents was associated with a 45% to 63% relative reduction in the risk of VTE compared with placebo.<sup>12,13</sup>

#### Pentasaccharides

Fondaparinux is a synthetic factor Xa antagonist that shares many features of LMWHs, including a high bioavailability and long half-life. Fondaparinux does not require monitoring, but it is contraindicated in patients with renal failure (CrCl < 30 mL/minute) and in patients weighing less than 50 kg.<sup>1</sup> Although PF4 antibodies have been associated with fondaparinux administration, this drug has not, to date, been associated with HIT.<sup>14</sup> The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS) trial demonstrated the advantage of fondaparinux over placebo in reducing the risk of VTE (Table 2).<sup>15</sup> The American College of Chest Physicians (ACCP) guidelines state that fondaparinux appears to be as effective and safe as LMWH.<sup>1</sup>

**TABLE 2. Anticoagulants for VTE Prophylaxis in Acutely Ill, Hospitalized Medical Patients**

| Trial   | Number of Patients | Agent (vs. placebo)                              | Detection of VTE   | Relative Risk Reduction                            | Number Needed to Treat |
|---------|--------------------|--|--|--|------------------------|
| MEDENOX | 866                | Enoxaparin 20 mg or 40 mg SC daily for 6-14 days | Distal and proximal venographic DVT or documented PE               | 63% (with 40 mg; 97.6 CI, 0.22-0.63; $P < 0.001$ ) | 10                     |
| PREVENT | 3706               | Dalteparin 5000 IU SC daily for up to 14 days    | CUS DVT, symptomatic VTE, and fatal PE                             | 45% (95% CI, 0.38-0.80; $P = 0.0015$ )             | 45                     |
| ARTEMIS | 849                | Fondaparinux 2.5 mg SC daily for 6-14 days       | Distal and proximal venographic DVT, symptomatic VTE, and fatal PE | 47% (95% CI, 0.077-0.693)                          | 20                     |

NOTE: Adapted from Samama et al,<sup>12</sup> Leizorovicz et al,<sup>13</sup> and Cohen et al.<sup>15</sup>

**Abbreviations:** ARTEMIS, Arixtra for Thromboembolism Prevention in a Medical Indications Study; CI, confidence interval; CUS, compression ultrasonography; DVT, deep vein thrombosis; MEDENOX, Prophylaxis in Medical Patients with Enoxaparin; PE, pulmonary embolism; PREVENT, Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial; SC, subcutaneously; VTE, venous thromboembolism.

### Vitamin K Antagonists

Vitamin K antagonists (VKAs) such as warfarin inhibit the production of prothrombin, clotting factors VII, IX, and X, and the anticoagulants protein C and protein S. Warfarin is challenging to manage because of its narrow therapeutic window, its tendency to exhibit considerable variability in dose-response, the time required to reach target international normalized ratio (INR), its potential for interaction with diet and concomitant medications, and its need for ongoing monitoring.<sup>5</sup> Warfarin should usually be initiated within the same 24 hours as parenteral anticoagulation, with a goal of achieving INR results between 2.0 and 3.0. An initial dose of 5 to 10 mg for the first 1 or 2 days is appropriate for most patients, and subsequent dosing should be based on INR response.<sup>5</sup> Warfarin prophylaxis is primarily used in patients in the US undergoing orthopedic surgery, including total hip replacement and hip and knee arthroplasty.<sup>1</sup>

### Future Anticoagulants

New oral agents have the potential to improve the management of patients who have a moderate to high risk of thromboembolic disease.

#### Rivaroxaban

This oral factor Xa inhibitor is showing promise in patients undergoing major orthopedic surgery. A prespecified pooled analysis was performed on data from the four Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism (RECORD) trials to evaluate the effect of rivaroxaban on the composite of symptomatic VTE (DVT or PE) and death, and bleeding. In the analysis, patients undergoing hip or knee arthroplasty had a VTE rate of 0.8% with rivaroxaban vs. 1.6% with enoxaparin, the current gold standard for surgical prophylaxis ( $P < 0.001$ ). Bleeding rates were not significantly different between treatment arms ( $P = 0.376$ ).<sup>16</sup>

#### Apixaban

This oral, direct, reversible factor Xa inhibitor is under evaluation for the prevention and treatment of VTE. In the Apixaban Prophylaxis in Patients Undergoing Total Knee Replacement Surgery (APROPOS) study of patients undergoing knee replacement, apixaban had a lower composite rate of DVT, PE, and all-cause mortality when compared with enoxaparin or warfarin.<sup>17</sup> In the ADVANCE-1 study of patients undergoing knee surgery, however, apixaban failed to meet criteria for noninferiority when compared with enoxaparin.<sup>18</sup> Apixaban is now being evaluated for VTE prophylaxis in acutely ill medical patients.

#### Dabigatran

This oral direct thrombin inhibitor reversibly binds to free and fibrin-bound thrombin. In the RE-NOVATE trial, dabigatran was noninferior to enoxaparin in reducing the events of DVT, PE, and all-cause mortality following total hip replacement surgery.<sup>19</sup> In a Phase II dose-ranging trial in patients with atrial fibrillation (Prevention of Embolic and Thrombotic Events in Patients with Persistent [AFPETRO]), dabigatran with or without aspirin was as effective as warfarin in reducing embolic events.<sup>20</sup> In the RE-MODEL study, dabigatran was as effective as enoxaparin in preventing VTE and all-cause mortality following knee replacement surgery, but failed to show equivalence to a higher dose of enoxaparin in the RE-MOBILIZE trial.<sup>21,22</sup> It should be noted that in the RE-MODEL study, enoxaparin was not administered at the dosage recommended by the U.S. Food and Drug Administration (FDA) for knee replacement surgery.

### Mechanical Prophylaxis

Mechanical methods of thromboprophylaxis include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and the venous foot pump (VFP). Mechanical approaches to thromboprophylaxis should be used primarily in patients who have a high risk of

**TABLE 3. Advantages and Limitations of Mechanical Thromboprophylaxis**

| Advantages   | Limitations   |
|--|---|
| <ul style="list-style-type: none"> <li>• Does not increase the risk of bleeding</li> <li>• Can be used in patients who have a high risk of bleeding</li> <li>• Efficacy has been demonstrated in a number of patient groups</li> <li>• May enhance the effectiveness of anticoagulant thromboprophylaxis</li> <li>• May reduce leg swelling</li> </ul> | <ul style="list-style-type: none"> <li>• Not as intensively studied as pharmacologic thromboprophylaxis (fewer studies and smaller)</li> <li>• No established standards for size, pressure, or physiologic features</li> <li>• Many specific mechanical devices have never been assessed in any clinical trial</li> <li>• Almost all mechanical thromboprophylaxis trials were unblinded and therefore have a potential for bias</li> <li>• Are less effective in high-risk groups than anticoagulant thromboprophylaxis</li> <li>• Greater effect in reducing calf DVT than proximal DVT</li> <li>• Effect on PE and death unknown</li> <li>• May reduce or delay the use of more effective anticoagulant thromboprophylaxis</li> <li>• Compliance by patients and staff is often poor</li> <li>• Trials may overestimate the protection compared with routine use</li> <li>• Cost associated with purchase, storage, dispensing, and cleaning of the devices, as well as ensuring optimal compliance</li> </ul> |

NOTE: Modified with permission from Geerts et al.<sup>1</sup>

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

bleeding or as an adjunct to pharmacotherapeutic prophylaxis.<sup>1</sup> The ACCP guidelines summarize the advantages and limitations of mechanical prophylaxis in patients at risk of developing VTE (Table 3).<sup>1</sup>

When properly fitted, GCS increase venous blood return through external pressure, thereby reducing venous stasis. IPC devices or sequential compression devices are usually applied over compression stockings. In addition to improving venous blood flow, these devices stimulate endogenous fibrinolysis. Compliance is often a problem in medical patients, who may not use the devices properly. Furthermore, for patients with severe vascular insufficiency (ankle brachial index <0.05), IPC may worsen vascular insufficiency and digital gangrene.

Inferior vena cava (IVC) filters are barrier devices that may benefit patients with major bleeding risk in the acute VTE setting by preventing PE. These devices, however, do not prevent DVT and may promote further venous stasis and clotting below the device. Importantly, patients with HIT should not have IVC filters placed due to a very high thrombogenic state that could lead to limb ischemia or cerulea phlegmasia dolens.<sup>23</sup>

## Thromboprophylaxis in Medical Patients

### Duration

Although major trials support the use of short-term prophylaxis—typically 6 to 14 days—in-hospital for acutely ill medical patients, the optimal duration of thromboprophylaxis in these patients is unclear.<sup>24</sup> The Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) trial is the first randomized trial to evaluate the potential benefits of extended prophylaxis in acutely ill medical patients. In this study, 5101 hospitalized patients with varying levels of reduced mobility due to cancer, ischemic stroke, heart failure, respiratory failure, infection, and other acute medical conditions received open-label enoxaparin 40 mg daily for a

mean duration of 10 days. Patients were then randomly assigned to additional therapy with enoxaparin or placebo for a mean duration of 28 additional days.<sup>25</sup> Preliminary findings from this trial suggest that high-risk medical patients can benefit from extended thromboprophylaxis following hospital discharge, with significantly reduced VTE events (RR reduction, 44%;  $P = 0.0011$ ). The benefits of thromboprophylaxis were apparent during the extended treatment period and persistent through 90 days.<sup>26</sup>

### Guideline Recommendations

Incorrect use of thromboprophylaxis does not stem from a lack of evidence-based recommendations. Within the past year, the ACCP, the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) have published updated guidelines for thromboprophylaxis in hospitalized patients at risk of VTE.<sup>1,27,28</sup> The 2008 ACCP guidelines include more than 700 recommendations for VTE risk assessment and management, to be implemented by a variety of physicians, including pulmonologists, cardiologists, cardiothoracic surgeons, and critical care medicine specialists.<sup>1</sup>

The ACCP guidelines organize prophylaxis recommendations on the basis of patient risk (Table 4).<sup>1</sup> Risk assessment remains relatively subjective, however, and validated risk assessment models are not yet widely available. The prudent approach is to consider thromboprophylaxis for all hospitalized medically ill patients who do not have a specific contraindication.

Key evidence-based recommendations regarding thromboprophylaxis for hospitalized, acutely ill patients include the following:<sup>1</sup>

- Every hospital should develop a formal strategy to address VTE prophylaxis;
- Aspirin alone is not recommended to prevent VTE for any patient group;

**TABLE 4. Guideline-Recommended Thromboprophylaxis for Hospitalized Patients by Level of VTE Risk**

| Levels of Risk   | Approximate DVT Risk Without Thromboprophylaxis (%) | Suggested Thromboprophylaxis Options  |
|--|---|---|
| Low risk<br>Minor surgery in mobile patients<br>Medical patients who are fully mobile  | < 10  | No specific thromboprophylaxis; early and “aggressive” ambulation   |
| Moderate risk<br>Most general, open gynecologic, or urologic surgery patients<br>Medical patients, bed rest or sick<br>Moderate VTE risk plus high bleeding risk | 10-40   | LMWH (at recommended doses), low-dose UFH bid or tid, fondaparinux<br>Mechanical thromboprophylaxis             |
| High risk<br>Hip or knee arthroplasty, HFS<br>Major trauma, SCI<br>High VTE risk plus high bleeding risk   | 40-80   | LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2-3)<br>Mechanical thromboprophylaxis |

NOTE: Modified with permission from Geerts WH, Bergqvist D, Pineo GF, et al.<sup>1</sup> Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines. 8th ed. *Chest* 2008; 133(6 suppl):381S-453S.

**Abbreviations:** bid, twice daily; DVT, deep-vein thrombosis; HFS, hip fracture surgery; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SCI, spinal cord injury; tid, three times daily; UFH, unfractionated heparin; VTE, venous thromboembolism.

- Mechanical methods of thromboprophylaxis should be used primarily for patients who have a high bleeding risk or possibly as an adjunct to anticoagulant thromboprophylaxis;
- Thromboprophylaxis with LMWH, UFH, or fondaparinux is recommended for patients admitted to hospital with an acute medical illness (Note: fondaparinux is recommended, but not FDA-approved, for this indication in the United States);
- On admission to the ICU, all patients should be assessed for risk of VTE, and most should receive thromboprophylaxis;
- All major trauma and all spinal-cord injury patients should receive thromboprophylaxis.

### Thromboprophylaxis in Surgical Patients

For hospitalized surgical patients, the ACCP guidelines indicate the importance of the type of surgery (eg, gynecologic, urologic, or neurologic) in determining the appropriate prophylaxis strategy. In general, routine thromboprophylaxis is recommended for patients undergoing major general, gynecologic, or orthopedic surgery, as well as bariatric and coronary artery bypass surgery.<sup>1</sup> Some specific recommendations regarding thromboprophylaxis for surgical patients include the following:

- Major general surgery: LMWH, low-dose UFH, or fondaparinux;
- Major gynecologic surgery and major open urologic procedures: LMWH, low-dose UFH, fondaparinux, and/or a mechanical device;
- Elective hip or knee arthroplasty: Anticoagulant therapy (LMWH, fondaparinux, or a VKA);
- Hip-fracture surgery: Fondaparinux, LMWH, a VKA, or low-dose UFH;

- Patients undergoing hip or knee arthroplasty or hip-fracture surgery should receive thromboprophylaxis for a minimum of 10 days; for hip arthroplasty and hip-fracture surgery, thromboprophylaxis should continue for more than 10 days and up to 35 days.

Although the ACCP guidelines recommend against aspirin monotherapy for any patient group, the American Academy of Orthopaedic Surgeons (AAOS) guidelines state that aspirin alone is an effective option in preventing VTE in “standard-risk” patients who are undergoing hip or knee replacement surgery.<sup>29</sup> However, evidence for aspirin monotherapy is currently limited.<sup>1</sup>

The 2008 ACCP guidelines include a new chapter on the perioperative management of patients receiving long-term antithrombotic treatment who must undergo surgery or other invasive procedures. To minimize surgical bleeding, the ACCP recommends the temporary discontinuation of antithrombotic treatment immediately before and during surgery for most patients. Discontinuing antithrombotics can increase the risk of a thromboembolic event, but this risk must be weighed against the risk of bleeding.<sup>1</sup> The guidelines also offer specific recommendations for the use of perioperative bridging therapy in patients receiving VKAs based on the risk of VTE and whether the patient has a mechanical heart valve or atrial fibrillation. Guidelines recommend discontinuing bridging anticoagulation 24 hours prior to surgery if therapeutic subcutaneous LMWH is the agent used and approximately 4 hours prior to surgery if intravenous UFH is the agent used.

### Thromboprophylaxis in Special Populations

Care must be taken when using thromboprophylaxis in certain high-risk populations. The following section provides recommendations regarding prophylaxis in the presence of

cancer, pregnancy, renal insufficiency, and epidural anesthesia.

### Cancer Patients

The ASCO and NCCN guidelines endorse the use of VTE prophylaxis with anticoagulants in all hospitalized patients with active cancer or suspicion of cancer in the absence of contraindications.<sup>27,28</sup> The ACCP guidelines restrict this recommendation to hospitalized cancer patients who are bedridden.<sup>1</sup> Thromboprophylaxis should continue at least through the duration of the hospital stay. Acceptable subcutaneous regimens include fondaparinux, dalteparin, or enoxaparin at the doses presented in Table 1; if UFH is chosen, the dose should be 5000 units every 8 hours.

Cancer patients who are scheduled to undergo major surgery require a different prophylaxis strategy. Even with prophylaxis, cancer patients have a 2-fold higher risk of postoperative VTE compared with noncancer patients and more than a 3-fold higher risk of fatal PE.<sup>30</sup> To manage this risk, the ASCO, NCCN, and ACCP guidelines recommend extended prophylaxis in patients undergoing major cancer surgery.<sup>1,27,28</sup> Specific recommendations include the following:

- All patients undergoing major surgical intervention for malignant disease should be considered for VTE prophylaxis with anticoagulants, with or without mechanical prophylaxis;
- Thromboprophylaxis should be initiated prior to the start of surgery or as early as possible following surgery;
- Mechanical interventions may supplement pharmacologic prophylaxis, especially in patients who have the highest risk;
- Prophylaxis with a LMWH should be initiated 12 to 24 hours after the surgical procedure;
- Continue prophylaxis at least 7 to 10 days postoperatively;
- Consider prolonged prophylaxis (ie, up to 4 weeks) with a LMWH for high-risk patients (eg, patients undergoing major abdominal or pelvic surgery, those with residual malignant disease after surgery, obese patients, and patients with a history of VTE).

Routine prophylaxis with anticoagulants is not recommended for most outpatients, except for those with high-risk factors (eg, thrombogenic chemotherapy or a central venous catheter). The strategy of restricting thromboprophylaxis to cancer outpatients with specific indications, however, may miss an opportunity to reduce VTE in this vulnerable patient population. In the PROTECHT study, 1166 ambulatory cancer patients were randomly assigned to placebo or the LMWH nadroparin for the duration of their chemotherapy. Treatment with nadroparin reduced the rate of clinical thrombosis by 47.2% compared with placebo (3.9% vs. 2.1%;  $P = 0.033$ ). The risk reduction was consistent across all measured events, including DVT, PE, stroke, and visceral venous thrombosis.<sup>31</sup>

### Pregnancy

Prophylaxis should be considered in pregnant women with known risk factors for VTE such as prior VTE, thrombophilia, and a history of prolonged immobility. In addition, women with a moderate to high risk of VTE associated with a cesarean section should be considered for postpartum thromboprophylaxis. For example, 1 of the following regimens may be appropriate for high-risk women following a cesarean section:<sup>32</sup>

- UFH 5000 units subcutaneously every 12 hours until fully mobile;
- LMWH subcutaneously once daily for 5 days (such as enoxaparin 20 mg daily).

For pregnant women already receiving anticoagulant prophylaxis (eg, for hypercoagulable state, structural heart disease, or prior DVT/PE), ACCP guidelines recommend discontinuing VKAs before 6 weeks of fetal gestation to minimize the risk of birth defects and miscarriage. In general, a LMWH should be substituted for VKAs as soon as pregnancy is confirmed or prior to conception in preparation for pregnancy, as VKAs cross the placental barrier, but LMWH and UFH do not.<sup>1,33</sup>

### Renal Insufficiency

The ACCP guidelines recommend that renal function be considered when making decisions about the use and/or dose of LMWHs and fondaparinux. Because these agents are eliminated primarily via renal clearance, changes in renal function can reduce drug clearance, prolong the half-life, and increase plasma concentrations. Consequently, the risk of treatment-related bleeding complications is elevated in patients with renal impairment.<sup>1</sup> Depending on the circumstances, one of the following options should be considered<sup>1</sup>:

- Avoid using an anticoagulant that bioaccumulates in the presence of renal impairment;
- Use a lower dose of the agent;
- Monitor the drug level or its anticoagulant effect.

In severe renal impairment (creatinine clearance < 30 mL/minute):<sup>7–10</sup>

- The prophylactic dose of enoxaparin should be adjusted to 30 mg subcutaneously once daily; no specific dosing adjustments have been recommended for dalteparin or tinzaparin;
- Fondaparinux is contraindicated.

### Epidural Anesthesia

Neuraxial blockade has several advantages over systemic opioids, but the risk of spinal or epidural hematoma may be increased with the concomitant use of antithrombotic drugs. Therefore, these agents must be used cautiously in patients with neuraxial blockade.<sup>1</sup> Guidelines from the

American Society of Regional Anesthesia and Pain Medicine (ASRA) contain the following recommendations:<sup>34</sup>

- Subcutaneous UFH: No contraindication, consider delaying heparin until after block if technical difficulty is anticipated;
- LMWH: Since twice daily dosing may be associated with an increased risk of spinal hematoma, delay initiation of LMWH until at least 24 hours after surgery, regardless of anesthetic technique; for single daily dosing, administer the first dose of LMWH 6 to 8 hours postoperatively and second dose no sooner than 24 hours after the first dose;
- Warfarin: Document normal INR after discontinuation (prior to neuraxial technique); remove catheter when INR  $\leq 1.5$  (initiation of therapy).

### Complications of Thromboprophylaxis

Before initiating thromboprophylaxis, it is important to evaluate the risk of bleeding, and patients should be assessed for contraindications that could increase that risk. HIT should also be considered.

### Bleeding Risk

The ACCP and ASCO guidelines emphasize the importance of weighing the potential benefits of thromboprophylaxis against the potential risks of bleeding in individual patients. According to the ACCP, the overall risk of bleeding with intravenous UFH in patients with VTE is less than 3%, and thromboprophylaxis has not been shown to increase the risk of bleeding compared with placebo in major clinical trials.<sup>13,15,35</sup> However, bleeding risk may increase in older patients and with higher doses of heparin. Warfarin therapy can be monitored with an INR to reduce the risk of bleeding during thromboprophylaxis.<sup>1</sup>

Anticoagulation therapy may be contraindicated in patients with certain factors and conditions that increase the risk of bleeding. These include:

- Clinically significant active or chronic bleeding;
- Recent central nervous system or spinal surgery with increased risk of bleeding;
- Thrombocytopenia (excluding HIT) or severe platelet dysfunction;
- Abnormalities associated with clotting factors.

The NCCN provides specific contraindications to anticoagulation therapy for the prevention and treatment of VTE in cancer patients.<sup>28</sup> These include:

- Recent central nervous system bleed; intracranial, or spinal lesions at high risk of bleeding;
- Active major bleeding ( $> 2$  units transfused in 24 hours);
- Chronic, clinically significant measurable bleeding for more than 48 hours;
- Thrombocytopenia (platelets  $< 50,000/\mu\text{L}$ );
- Severe platelet dysfunction;
- Recent major operation with high risk of bleeding;

- Underlying coagulopathy (eg, clotting factor abnormalities or elevated prothrombin time or activated partial thromboplastin time [aPTT]);
- Spinal anesthesia or lumbar puncture;
- High risk of falls.

### HIT

HIT is a serious complication that can occur as a result of exposure to heparin. It is an immune response that causes platelet activation and platelet aggregation, among other effects, and is capable of leading to severe thrombosis, amputation, or death.<sup>36</sup> The incidence of HIT varies with subpopulations of patients and more commonly develops in patients receiving heparin in therapeutic doses. Early diagnosis (through an interpretation of clinical and laboratory information) is important to improve clinical outcomes, but difficult to achieve.<sup>36</sup> The ACCP guidelines note that enzyme-linked immunosorbent assay (ELISA)-based tests for HIT are often falsely positive after surgery. As an alternative, serotonin-release tests are more specific, although they are not as widely available.<sup>1</sup>

Substantial clinical evidence suggests that LMWH poses less of a risk of HIT than UFH. Martel et al,<sup>37</sup> for example, conducted a meta-analysis of 15 randomized and non-randomized controlled trials (a total of 7287 patients) that included studies that compared prophylactic doses of UFH and LMWH and assessed postoperative or medical inpatients who received prophylaxis. The analysis revealed that the risk of HIT was 2.6% following UFH use compared with 0.2% following LMWH use.<sup>37</sup> Despite the inclusion of UFH in the ASCO guidelines, ASCO acknowledges that a lower risk of HIT is one of the potential advantages of LMWH over UFH in cancer surgery prophylaxis.<sup>27</sup> In addition, the recommendation to transition to outpatient therapy as soon as possible is an indirect way of stating a preference for LMWH. For cancer patients with established VTE, the recommendation is more direct: LMWH is clearly preferred over UFH for both initial and continuing antithrombotic therapy.<sup>27</sup>

### Conclusions

Thromboprophylaxis should be considered in all hospitalized patients who have a risk of VTE. Anticoagulants are the mainstays of prophylaxis, and recent clinical trials have clearly demonstrated the efficacy of LMWHs and fondaparinux in preventing VTE. Each class of anticoagulant carries a number of side effects and contraindications, and frequent patient evaluation and monitoring may be required. This is especially true in those with renal impairment, for whom UFH may be a logical choice. A number of organizations have released guidelines for VTE prophylaxis that provide specific recommendations regarding thromboprophylaxis in special patient populations and scenarios.

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