

# Prevention of Thrombosis with Warfarin, Aspirin, and Mechanical Methods

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**Venous thromboembolism (VTE) is a serious disorder and a major cause of morbidity and mortality among acutely ill medical patients. However, despite the growing number of patients with acute medical illnesses who have an associated risk of VTE, the widespread use of VTE prophylaxis does not yet occur for both surgical and nonsurgical patients. Although individuals at greatest risk for VTE include patients undergoing major orthopedic surgery and those with medical conditions that require prolonged immobilization, all patients who have acute medical illnesses should be considered for VTE prophylaxis. Several strategies, including various mechanical and pharmacologic approaches, are currently used for VTE prophylaxis. Increased awareness about the full range of options for VTE prophylaxis can help health care providers select the appropriate course of action to help reduce the incidence of VTE among patients with acute medical illnesses. (*Clinical Cornerstone*. 2005;7[4]:49–56) Copyright © 2005 Excerpta Medica, Inc.**

Two million people each year are affected by venous thromboembolism (VTE) in the United States, making it the third most common cardiovascular disease after coronary heart disease and stroke.<sup>1</sup> VTE includes the development of deep vein thrombosis (DVT) and pulmonary embolism (PE); of the estimated 600,000 Americans each year who develop PE, 60,000 people will die of this complication.<sup>2</sup> DVT and PE can develop spontaneously, or they can result from medical circumstances such as surgery, prolonged bed rest, or trauma. Several strategies, including mechanical and pharmacologic approaches, are currently available for VTE prophylaxis (**Table I**).<sup>3</sup>

Recently, several new anticoagulants have been evaluated in Phase III trials. The Thrombin Inhibitor in Venous thromboEmbolism (THRIVE) Treatment Study, for example, found that the oral direct thrombin inhibitor (DTI) ximelagatran was as effective as standard enoxaparin/warfarin treatment for the prevention of recurrent VTE.<sup>4</sup> In this study of 2489 patients with acute DVT (of which one third had concomitant PE), VTE recurred in 26 of the 1240 patients assigned to receive 6 months of treatment with ximelagatran (estimated cumulative risk, 2.1%) and

in 24 of the 1249 patients assigned to receive 6 months of treatment with enoxaparin/warfarin (estimated cumulative risk, 2.0%).

Another randomized trial evaluated the efficacy and safety profile of the low-molecular-weight heparin (LMWH) fondaparinux compared with the LMWH enoxaparin followed by warfarin in patients with acute DVT.<sup>5</sup> At 3 months, symptomatic VTE had recurred in 3.9% of patients who had received fondaparinux and in 4.9% of patients who had received enoxaparin and warfarin, demonstrating the noninferiority of fondaparinux in these patients. Major bleeding was recorded in about 1% of the patients in both groups. Several other studies are now under way to assess newer agents indicated for the prevention of VTE.

Currently, the use of an LMWH followed by a vitamin K antagonist, such as warfarin, for up to 6 months is appropriate for use in preventing thrombus formation and embolism in most patients<sup>6</sup>; however, some patients, such as those at risk for heparin-induced thrombocytopenia or excessive bleeding, may benefit from other approaches. These alternative strategies are addressed in the current discussion.

**TABLE I. MECHANICAL AND PHARMACOLOGIC PREVENTATIVE MEASURES FOR VENOUS THROMBOEMBOLISM (VTE).**

Practice	Type	Description	Comment
Graduated elastic stockings	Mechanical	Fitted hose that extend above the knee	Fitted hose are more efficacious than nonfitted
Intermittent pneumatic compression	Mechanical	Devices fitted over lower extremities that sequentially inflate and deflate	
Aspirin	Pharmacologic	Usually 325 mg/d	
Warfarin	Pharmacologic	5–10 mg started the day of or after surgery; adjust to achieve an INR of 2–3	Monitoring of INR needed
Low-dose unfractionated heparin	Pharmacologic	Generally 5000 U SC BID or TID, though some studies have adjusted dose to maintain partial thromboplastin time at high end of normal	Contraindicated if active bleeding or history of thrombocytopenia; no need to follow coagulation studies (unless adjusted dose is used)
Low-molecular-weight heparin	Pharmacologic	Dose depends on agent used, type of surgery, and VTE risk	No need to monitor coagulation studies
DTI	Pharmacologic	Dose depends on agent used, type of surgery, and VTE risk	DTI pharmacodynamics are monitored by the aPTT, with a target aPTT ratio from 1.5–2.5 or 3.0

INR = international normalized ratio; DTI = direct thrombin inhibitor; aPTT = activated partial thromboplastin time. Adapted with permission.<sup>3</sup>

### WARFARIN FOR THROMBOPROPHYLAXIS

Warfarin has been a cornerstone of oral anticoagulant therapy for more than 50 years. It has been used to prevent DVT and PE; its effectiveness has been clearly established in randomized clinical trials.<sup>7</sup> Warfarin also is indicated for the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, for the primary prevention of acute myocardial infarction in high-risk patients, and for the prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction.<sup>8</sup>

Warfarin can be used for long-term thromboprophylaxis, due to convenient oral administration and its low cost. However, warfarin is difficult to use for many reasons. These include variability in dose response (the patient's international normalized ratio [INR] must be monitored regularly when using this agent [Table IIA and Table IIB]),<sup>9</sup> a narrow therapeutic window, the potential for interaction with other drugs (Table III),<sup>10</sup> and standardization issues.

American College of Chest Physicians (ACCP) guidelines issued in 2004 regarding the use of warfarin and other

vitamin K antagonists for anticoagulation carry recommendations with a status of Grade 2B or 2C, meaning that the benefit-to-risk ratio is not clear-cut for all patients and that the supportive evidence comes from randomized clinical trials with inconsistent results or methodologic weaknesses or from observational studies.<sup>8</sup> Current recommendations indicate that vitamin K antagonists should be started at doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the patient's

### KEY POINT

**Current recommendations indicate that vitamin K antagonists should be started at doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the patient's INR response.**

**TABLE IIA. WARFARIN STARTING DOSE.**

Patient Group	Recommendations	Grade
Most patients	<ul style="list-style-type: none"> <li>• 5–10 mg QD for the first 1–2 days</li> <li>• Thereafter, adjust by INR</li> </ul>	2B
Patients >60 years old	<ul style="list-style-type: none"> <li>• ≤5 mg QD to start</li> <li>• Thereafter, adjust by INR</li> </ul>	2C
Patients who:	<ul style="list-style-type: none"> <li>• ≤5 mg QD to start</li> <li>• Thereafter, adjust by INR</li> </ul>	2C
<ul style="list-style-type: none"> <li>• are debilitated</li> <li>• are undernourished</li> <li>• have liver disease</li> <li>• have congestive heart failure</li> </ul>		

The guidelines recommend the following monitoring frequency for patients in the community:

- Start INR monitoring after the first 2–3 doses (Grade 2C)
- Monitor INR every few days until stable (at least 2 consecutive INRs stable)
- Then, decrease frequency of monitoring gradually, using clinical judgment; interval between INRs should not be longer than 4 weeks (Grade 2C)

INR = international normalized ratio.  
Adapted with permission.<sup>9</sup>

**TABLE IIB. WARFARIN DOSAGE ADJUSTMENT WHEN THE INTERNATIONAL NORMALIZED RATIO (INR) IS ELEVATED.**

INR	Recommendations	Grade
Above therapeutic range but <5.0	<ul style="list-style-type: none"> <li>• Skip a dose (or lower the dose) and monitor more frequently. Start at a lower dose when INR therapeutic.</li> <li>• If minimally above therapeutic range, no dose adjustments may be needed.</li> </ul>	2C
INR ≥5.0 and <9.0 no significant bleeding	<ul style="list-style-type: none"> <li>• Skip the next 1–2 doses, monitor more frequently, and start at a lower dose when INR therapeutic.</li> <li>• Or, skip the next dose and give vitamin K (≤5 mg orally for rapid reversal). This will lower the INR within 24 hours. If the INR is still high, give an additional 1–2 mg of vitamin K orally. Start warfarin at a lower dose when INR therapeutic.</li> </ul>	2C
INR ≥9.0 no significant bleeding	<ul style="list-style-type: none"> <li>• Hold warfarin and give vitamin K (5–10 mg orally). This will lower the INR within 24–48 hours. If the INR is still high, give additional vitamin K orally. Start warfarin at a lower dose when INR therapeutic.</li> </ul>	2C
INR any value above therapeutic range, serious bleeding	<ul style="list-style-type: none"> <li>• Hold warfarin and give vitamin K (10 mg by slow IV infusion). Vitamin K can be repeated every 12 hours. May also give fresh plasma and prothrombin complex concentrate (or recombinant factor VIIa).</li> </ul>	1C
Life-threatening bleeding	<ul style="list-style-type: none"> <li>• Hold warfarin and give prothrombin complex concentrate and vitamin K (10 mg by slow IV infusion).</li> </ul>	1C

Note: INR values >4.5 are less reliable than values closer to the therapeutic range, so these recommendations are an approximate guide. When warfarin therapy is started or changed, frequent INR monitoring is needed (up to twice weekly). Adapted with permission.<sup>9</sup>

**TABLE III. DRUGS THAT ALTER RESPONSE TO WARFARIN.**

Increase INR		Decrease INR
Phenytoin*	Amiodarone†	Phenobarbital†
Metronidazole†	Cimetidine†	Rifampin/rifabutin†
Fluconazole†	Erythromycin†	Carbamazepine*
Itraconazole†	Dong quai*	Vitamin K†
Ketoconazole†	Statins*	Phenytoin* (chronic use)
Sulfamethoxazole/ trimethoprim†	Alcohol‡	Sucralfate*
		Ginseng*
		Alcohol‡

INR = international normalized ratio.

\*Moderate interaction.

†Severe interaction.

‡Effect of alcohol on INR is unpredictable, may increase/decrease INR. For a detailed review, see Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med.* 2005;165:1095–1106.

Adapted with permission.<sup>10</sup>

Note: This list is not all-inclusive; each patient's INR should be monitored after initiating or modifying any drug therapy.

INR response (Table IV).<sup>11</sup> An INR of 2.0 to 3.0, which is considered moderate or standard intensity, remains the target range for most patients needing therapy with a vitamin K antagonist.<sup>8</sup>

Since the most common complication of warfarin therapy is bleeding, studies have evaluated whether a lower-intensity dose of warfarin is as effective and safe as a conventional-intensity dose. One recent analysis evaluated 738 patients who were randomly assigned to continue warfarin therapy with a target INR of 2.0 to 3.0 (conventional intensity) or a target INR of 1.5 to 1.9 (low intensity). Patients were followed for an average of 2.4 years. Researchers found that conventional-intensity warfarin therapy was more effective than low-intensity warfarin therapy and that using a lower dose did not reduce the risk of clinically important bleeding.<sup>12</sup> Furthermore, major bleeding episodes were reported in 9 patients in the low-dose group and 8 patients in the conventional group.

Long-term low-intensity warfarin (target INR, 1.5–2.0) has been found in clinical studies to be effective in preventing recurrent VTE.<sup>13</sup> Ridker et al<sup>13</sup> randomized 508 patients with idiopathic VTE who had received full-dose anticoagulation therapy to receive placebo or low-intensity warfarin. Patients were followed for a median of 6.5 months, monitored for recurrent VTE, major hemorrhage, and death. Of the 253 patients in the placebo group, 37 had

recurrent VTE compared with 14 of 255 patients receiving warfarin, indicating a risk reduction of 64% with warfarin treatment (hazard ratio, 0.36 [95% CI, 0.19–0.67];  $P < 0.001$ ). Low-intensity warfarin was associated with a 48% reduction in a composite end point of recurrent VTE, major hemorrhage, and death, compared with placebo. In addition, the number of occurrences of major hemorrhage (5 of 255 patients in the low-intensity warfarin groups vs 2 of 253 patients in the placebo group;  $P = 0.25$ ) and death (4 of 255 patients vs 8 of 253 patients, respectively;  $P = 0.26$ ) was not significantly different when comparing low-intensity warfarin and placebo.<sup>13</sup>

Warfarin will likely remain an important agent for the prevention of VTE, providing several benefits such as low cost and ease of administration. However, further studies of warfarin in combination with LMWHs and DTIs are clearly warranted.

### ASPIRIN FOR THROMBOPROPHYLAXIS

Although aspirin is an antiplatelet agent that can help prevent blood from clotting inside the blood vessels,<sup>14,15</sup> aspirin alone is not recommended for thromboprophylaxis for several reasons. First, studies supporting the use of antiplatelet drugs for VTE are limited. Second, numerous trials have found a lack of benefit or inferior results with aspirin therapy.<sup>16,17</sup> In addition, aspirin therapy increases the risk of major bleeding, especially when combined with other agents.<sup>7</sup>

The Pulmonary Embolism Prevention trial—a randomized placebo-controlled trial of 13,356 patients undergoing surgery for hip fracture in hospitals located in Australia, New Zealand, South Africa, Sweden, and the United Kingdom—found that low-dose aspirin reduces the risk of PE (including fatal events) and symptomatic DVT.<sup>15</sup> Patients received 160 mg/d of aspirin or placebo starting before surgery and continued treatment for 35 days, receiving

### KEY POINT

**Although aspirin is an antiplatelet agent that can help prevent blood from clotting inside the blood vessels, aspirin alone is not recommended for thromboprophylaxis.**

**TABLE IV. SUGGESTED TREATMENT STRATEGIES FOR VARIOUS INTERNATIONAL NORMALIZED RATIO (INR) VALUES IN PATIENTS RECEIVING WARFARIN ADMINISTERED TO ACHIEVE A TARGET INR OF 2.0 TO 3.0.**

INR Value	Clinical Data	Treatment Strategy
Any elevation	Life-threatening bleeding	<ol style="list-style-type: none"> <li>1. Withhold warfarin.</li> <li>2. Replace coagulation factors using plasma or complex concentrates.</li> <li>3. Administer IV vitamin K (5–10 mg, with the dose depending on the INR).</li> <li>4. Correct mechanical causes of hemorrhage.</li> <li>5. Provide medical support, including transfusion, as required.</li> </ol>
Any elevation	Major (non-life-threatening bleeding)	<ol style="list-style-type: none"> <li>1. Withhold warfarin.</li> <li>2. Consider administration of plasma or complex concentrates.</li> <li>3. Administer IV vitamin K (1–10 mg, with the dose depending on the INR).</li> <li>4. Correct mechanical causes of hemorrhage.</li> <li>5. Provide medical support, including transfusion, as required.</li> </ol>
4.5–6.0	No bleeding	<ol style="list-style-type: none"> <li>1. Withhold warfarin and recheck INR in 24–48 hours OR</li> <li>1. Withhold warfarin, administer 1 mg oral vitamin K and recheck INR in 24–48 hours OR</li> <li>1. Reduce warfarin dose, recheck INR in 24–48 hours.</li> </ol>
6.1–10.0	No bleeding	<ol style="list-style-type: none"> <li>1. Withhold warfarin and recheck INR in 24 hours OR</li> <li>1. Withhold warfarin, administer 1 mg oral vitamin K and recheck INR in 24 hours OR</li> <li>1. Withhold warfarin, administer 1–2.5 mg of oral vitamin K, consider using plasma or complex concentrates ONLY IN PATIENTS AT HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours.</li> </ol>
10.1 and above	No bleeding	<ol style="list-style-type: none"> <li>1. Withhold warfarin, administer 1–5 mg of oral vitamin K and recheck INR in 24 hours OR</li> <li>1. Withhold warfarin, administer 0.5–1.0 mg of IV vitamin K and recheck INR in 24 hours OR</li> <li>1. Withhold warfarin, administer 1–5 mg of oral vitamin K, consider using plasma or complex concentrates ONLY IN PATIENTS AT HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours OR</li> <li>1. Withhold warfarin, administer 0.5–1.0 mg of IV vitamin K, consider plasma or complex concentrates ONLY IN PATIENTS WITH HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours.</li> </ol>

Note: For patients receiving warfarin with a higher target INR, the ranges presented should be adjusted upward. In all cases, the cause of the excessive prolongation of the INR should be sought and corrected. Adapted with permission.<sup>11</sup>

additional thromboprophylaxis as needed. Among patients with hip fracture taking aspirin, risk of PE was reduced by 43% (95% CI, 18–60;  $P = 0.002$ ) and symptomatic DVT was reduced by 29% (95% CI, 3–48;  $P = 0.03$ ), compared with placebo. No increase in death rate was observed in the aspirin group, although the number of postoperative transfused bleeding episodes was higher in the group taking aspirin ( $P = 0.04$ ).<sup>15</sup>

LMWH was found to be more effective than aspirin in high-risk subjects, according to the findings of the LONFLIT3 study that evaluated methods of DVT pre-

vention in high-risk subjects after long (>10 hours) air-plane flights.<sup>18</sup> A total of 300 participants at high risk for DVT were randomized into 3 groups: 1 group received no treatment; 1 group received 400 mg of oral, soluble aspirin QD for 3 days (starting 12 hours before the beginning of the flight); or 1 group received 1 weight-adjusted dose of the LMWH enoxaparin, injected 2 to 4 hours before the flight. The incidence of DVT was 4.82% in the control group and 3.6% in the aspirin group; in the LMWH group, 0.6% of patients experienced thrombotic events ( $P < 0.002$  compared with the other 2 groups).

Mild gastrointestinal symptoms were reported in 13% of the patients who received aspirin therapy.

## MECHANICAL METHODS FOR VTE PROPHYLAXIS

Mechanical methods of thromboprophylaxis are intended to increase venous outflow from the legs and/or reduce blood stasis within leg veins and are attractive primarily due to the absence of bleeding risk compared with pharmacologic agents. As a result, these methods are particularly useful for patients at high risk of bleeding. They are also suitable for chronically bedridden patients, in whom prolonged therapy with heparins may be problematic due to bleeding risk or osteoporosis. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy recommends mechanical prophylaxis in case of contraindication to anticoagulant therapy in nonsurgical patients.<sup>19</sup>

Efficacy studies comparing the use of mechanical prophylaxis (such as graduated compression socks, pneumatic compression devices, and venous foot pumps) versus the use of pharmacologic anticoagulation approaches in nonsurgical patients are lacking to date.<sup>20</sup> However, mechanical prophylaxis is often used with anticoagulation therapy to improve effectiveness.<sup>21,22</sup> Several studies have shown that the use of compression socks or elastic stockings is advantageous in patients with myocardial infarction<sup>23</sup> or in reducing DVT following acute stroke.<sup>24</sup>

### KEY POINT

**Mechanical prophylaxis is often used with anticoagulation therapy to improve effectiveness.**

A study that analyzed the outcomes of a total of 1892 patients who were treated with intermittent pneumatic compression following gynecologic surgery found that patients who were most likely to fail intermittent pneumatic compression prophylaxis included those patients with cancer, patients with a history of DVT, and patients at age  $\geq 60$  years.<sup>25</sup> Researchers concluded that patients with more than 1 of these independent risk factors should be considered for more intense prophylaxis regimens.<sup>25</sup>

The effectiveness and safety of mechanical versus LMWH approaches for DVT prophylaxis have been

compared in patients after total hip replacement.<sup>26</sup> A total of 216 patients were randomized for DVT prophylaxis management with either the use of a foot pump or LMWH, resulting in 200 patients available for analysis (16 patients were excluded because they either did not tolerate the continuous use of the foot pump or the use of LMWH). DVT was detected by serial duplex sonography in 3 of 100 patients in the foot-pump group and in 6 of 100 patients in the LMWH group ( $P < 0.05$ ). In addition, the mean postoperative drainage was lower in the foot-pump group (259 mL vs 328 mL;  $P < 0.05$ ), and they had less swelling of the thigh (10 mm compared with 15 mm;  $P < 0.05$ ). Researchers concluded that mechanical prophylaxis of DVT after total hip replacement was effective and safe.<sup>26</sup>

The issue of adequate patient compliance with mechanical devices warrants consideration; some patients find these methods difficult to tolerate. For example, a study by Westrich and Sculco<sup>16</sup> showed that the degree of compliance among 122 patients who experienced total knee arthroplasty was associated with the prevalence of DVT after surgery—no DVT was present in patients with an average of 80% compliance with the use of pneumatic plantar compression, but a significant incidence of DVT was observed in patients averaging 55% compliance.

A study by Robertson et al<sup>27</sup> evaluated a consecutive series of patients undergoing total joint arthroplasty who were sequentially treated with 2 mechanical devices designed to prevent DVT. One group of 104 patients wore a thigh-high sequential compression device. The second group of 120 patients wore a foot pump. As measured by responses to a questionnaire, patient satisfaction among patients using the foot pump was significantly higher than for those using the sequential compression device (73% vs 55%, respectively). The study also found a higher degree of compliance among patients using the foot pumps as compared with patients using the sequential compression device.<sup>27</sup>

Filter placement within the inferior vena cava (IVC) can be an effective intervention for VTE prophylaxis in certain patients. Although IVC filters do not prevent DVT, they can prevent PE.<sup>28</sup> Two recent studies (a study of 94 patients with multiple trauma who underwent placement of temporary IVC filters in 2002/2003 and another study of 88 multiple-trauma patients who received temporary IVC filter placement at the intensive care unit bedside from 2002 to 2004) found that this

approach was simple and safe, prevented fatal PE, and served as an effective bridge to anticoagulation therapy until other VTE prophylaxis measures could be taken.<sup>28,29</sup>

A decision to use IVC filters is based on several considerations, including the patient's clinical condition, the type of filter available, the alternative access sites available, and the expertise of the physician.<sup>30</sup> Approximately 30,000 to 40,000 IVC filters are placed in patients each year in the United States, particularly in about 50% of trauma patients.<sup>31</sup> IVC filters are often considered when a clear contraindication to anticoagulant therapy exists or when VTE occurs despite adequate anticoagulation.<sup>31</sup> However, vena cava interruption is often regarded as an incomplete treatment for VTE because, unlike anticoagulant therapy, it offers no beneficial effect on the prevention of DVT or the prevention of DVT extension, recurrence, and subsequent postthrombotic syndrome.<sup>32</sup> Therefore, physicians recommend the use of IVC filters selectively in patients with contraindications to anticoagulants or those with recurrent PE despite adequate anticoagulation. Whenever possible, pharmacologic anticoagulation is the preferred approach to VTE prophylaxis in patients at risk for VTE.

### KEY POINT

**IVC filters are often considered when a clear contraindication to anticoagulant therapy exists or when VTE occurs despite adequate anticoagulation.**

### CONCLUSIONS

The use of VTE prophylaxis is justified by the often clinically silent presentation of VTE and its high prevalence among hospitalized patients. VTE is diagnosed in ~170,000 incident cases among hospitalized patients in the United States each year; >20,000 patients die of VTE before discharge.<sup>33</sup> VTE prophylaxis is clearly the most cost-effective strategy for managing DVT and PE.<sup>34</sup> At greatest risk are patients undergoing major orthopedic surgery and those with medical conditions that require immobilization for 5 days or longer. Strategies currently used to prevent VTE include anticoagulant therapy with heparin (LMWH or unfractionated heparin), DTIs, oral

anticoagulants such as warfarin, and mechanical methods. For patients undergoing total hip or knee replacement, treatment with adjusted-dose warfarin, LMWH, or fondaparinux may be used. Warfarin has been the leading oral anticoagulant agent for various thromboembolic events. The DTI ximelagatran—the first clinically tested oral anticoagulant since the introduction of warfarin in the early 1940s—is currently being evaluated for use in the United States for the prevention and treatment of VTE.

### KEY POINT

**VTE prophylaxis is clearly the most cost-effective strategy for managing DVT and PE.**

Several randomized clinical trials have evaluated the efficacy of pharmacologic prophylaxis, with only a limited number of studies that have assessed the efficacy of mechanical prophylaxis. More studies are needed to assess various approaches to achieve maximal prevention of VTE.

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