



# Venous Thromboembolism Following Major Orthopedic Surgery: What is the Risk After Discharge?

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## Abstract

Guidelines recommend thromboprophylaxis for at least 10 days to prevent venous thromboembolism in patients undergoing high-risk orthopedic surgery, such as total hip arthroplasty (THA) or total knee arthroplasty (TKA). Furthermore, the recently updated ACCP guidelines also recommend extending the duration of thromboprophylaxis for 28 to 35 days following THA or hip fracture surgery as the risk for venous thromboembolism persists for up to 3 months after surgery. Extended-duration thromboprophylaxis (up to 6 weeks) with low-molecular-weight heparin is significantly more effective in preventing venous thromboembolism in orthopedic surgery patients than the recommended practice of at least 10 days. Extended-duration thromboprophylaxis may require risk stratification to identify high-risk patients. Current risk-assessment models have limitations and are not specific to orthopedic surgery patients; therefore, improvements may facilitate the use of extended-duration thromboprophylaxis in high-risk patients, thereby reducing the burden of venous thromboembolism.

Venous thromboembolism, including both deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important complication of major orthopedic surgery, and is associated with significant morbidity and mortality.<sup>1</sup> Current data suggest that, in the absence of thromboprophylaxis, venographically documented DVT occurs in approximately 50% of patients undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA), and fatal PE may occur in up to 1.7% of patients undergoing TKA and up to 2% of those undergoing THA (Table 1). Approximately half of all cases of DVT after orthopedic surgery involve proximal leg veins.<sup>1,3</sup> Therefore, patients undergoing major orthopedic surgery, such as TKA or THA, are at high risk or very high risk of venous thromboembolism; hence, current management guidelines recommend that thromboprophylaxis should be used routinely in such patients.<sup>2,3</sup>

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Despite the existence of national and international guidelines, thromboprophylaxis is inadequately used in orthopedic surgery patients. In one study, only 19% of high-risk patients in non-teaching hospitals and 44% of those in teaching hospitals received adequate thromboprophylaxis.<sup>4</sup> More recently, a review of the medical records of 10 US hospitals showed that the percentage of patients receiving appropriate thromboprophylaxis according to the American College of Chest Physicians (ACCP 1995) guidelines was 84% for THA, 76% for TKA, and 45% for hip fracture surgery.<sup>5</sup> The significance of such underuse of therapy is underlined by the fact that PE remains the most common preventable cause of death in hospitalized patients<sup>6</sup>; data suggest that approximately 20,000-30,000 deaths could be prevented each year in the United States alone by the use of appropriate thromboprophylaxis.<sup>6,7</sup>

A number of factors contribute to the inadequate use of thromboprophylaxis in this patient group.<sup>3,6,7</sup> First, the incidence of symptomatic thromboembolic events is relatively low, 5%, during the perioperative period.<sup>8</sup> As a result, some surgeons may consider DVT or PE to be rare complications that do not warrant thromboprophylaxis.<sup>7</sup> Yet, post-thrombotic complications generally develop over a period of months or years after an acute venous thrombosis, and usually are treated by vascular specialists. Second, concern about potential bleeding complications during anticoagulant therapy may limit the use of thromboprophylaxis.<sup>6,7</sup> However, extensive data from meta-analyses and controlled clinical trials have shown that this risk is largely overestimated: the risk of clinically important bleeding either is not increased or increased only slightly in patients receiving prophylactic doses of low-molecular-weight heparin, low-dose unfractionated heparin, or a vitamin K antagonist.<sup>3</sup> Sufficient evidence exists that shows that appropriately used thromboprophylaxis has a desirable risk/benefit ratio and is cost-effective. Therefore, thromboprophylaxis provides an opportunity to

improve patient outcome and reduce hospital costs.<sup>3</sup>

Improved education about the risks of venous thromboembolism is central to overcoming clinicians' reservations regarding the use of thromboprophylaxis and increases the use of such therapy.<sup>6,7,9</sup> Despite the use of recommended thromboprophylaxis, however, some high-risk patients (particularly those undergoing THA or TKA) remain at significant risk for DVT.<sup>9</sup> In a recent meta-analysis, the 3-month incidence of nonfatal, symptomatic venous thromboembolism and fatal PE was 3.2% and 0.1%, respectively, in patients receiving short-term thromboprophylaxis (7-10 days) after THA or TKA.<sup>10</sup> Accurate risk assessment therefore is necessary both to identify high-risk patients who might benefit from prolonged thromboprophylaxis, and to prevent the overuse of therapy in patients at moderate or low risk, which may incur increased bleeding risk. Risk assessment also may be useful in the diagnosis of venous thromboembolism and in identifying risk factors that may be used to guide decisions about the duration of thromboprophylaxis.<sup>9</sup>

Accurate risk assessment is difficult, however. In an individual patient, the level of risk will depend on a variety of interacting clinical-setting-related (exposing or procedural) and patient-related (clinical, inherited, or acquired) risk factors, described below. Nevertheless, in view of the substantial costs of treating venous thromboembolism,<sup>11</sup> effective risk stratification and targeting of thromboprophylaxis to patients at a higher risk is essential to optimize the clinical efficacy and cost-effectiveness of thromboprophylaxis. It can be anticipated that this process may lead to increased understanding of specific risk factors, which, together with the emergence of new therapeutic strategies, will necessitate the continuous updating of existing consensus guidelines.

TABLE 1				
Incidence of Venous Thromboembolism in Major Orthopedic Surgery Patients Not Receiving Thromboprophylaxis* <sup>2</sup>				
Surgery	Total DVT (%)	Proximal DVT (%)	Total PE (%)	Fatal PE (%)
THA	42-57	18-36	0.9-28	0.1-2.0
TKA	41-85	5-22	1.5-10	0.1-1.7
Hip fracture surgery	46-60	23-30	3-11	2.5-7.5

*Abbreviations: DVT=deep vein thrombosis, PE=pulmonary embolism, THA=total hip arthroplasty, and TKA=total knee arthroplasty.*  
*\*Deep vein thrombosis rates are based on mandatory venography in prospective clinical trials published since 1980 in which patients received either placebo or no prophylaxis. Pulmonary embolism rates were derived from prospective studies that may have included prophylaxis.*

### Risk of Venous Thromboembolism In Orthopedic Patients

The overall incidence of DVT in patients undergoing THA or TKA without thromboprophylaxis is approximately 50%, of which approximately half are proximal deep vein thrombi, but the incidence varies according to the surgical procedure (Table 1). Evidence-based reviews and consensus guidelines suggest that in the absence of thromboprophylaxis, the incidence of total and proximal DVT in patients undergoing TKA ranges from 40%-85% and 5%-22%, respectively, and for patients undergoing THA, 42%-60% and 16%-36%, respectively.<sup>1-3,11,12</sup>

The incidence of asymptomatic PE is less clear, however.<sup>3</sup> In the aforementioned studies, the incidence of total and fatal PE was estimated to be 1.5%-10% and 0.1%-1.7% in patients undergoing TKA, respectively, and 0.7%-30% and 0.1%-4% in those undergoing THA, respectively.<sup>1-3,11,12</sup> These figures are consistent with the results of a prospective study involving >6500 patients, in which the overall incidence of PE during a first hospitalization was estimated to be 0.9%, with an incidence of between 0.4% and 3% depending on the level of risk.<sup>13</sup> In another study, symptomatic DVT or PE was diagnosed in 2.1% and 2.8% of patients after primary TKA or THA, respectively.<sup>14</sup> Even more striking is the fact that the events were diagnosed after hospital discharge in 47% and 76% of patients undergoing TKA or THA, respectively.

In patients undergoing hip fracture surgery, although the incidences of total and proximal DVT (46%-60% and 23%-30%, respectively) are comparable with those in patients undergoing THA and TKA, the incidence of PE is markedly higher.<sup>1-3,11,12</sup> The overall incidence of PE in patients undergoing hip fracture surgery has been estimated to be between 3% and 24%, while fatal PE has been reported to be between 2.5% and 13% of patients.<sup>1-3,11,12</sup>

In addition to the high risks of venous thromboembolism associated with arthroplasty, recent data have shown that some patients

undergoing arthroscopy have a significant risk for venous thromboembolism. In one study, venographically confirmed DVT was present in 18% of patients one week after knee arthroscopy.<sup>15</sup> Routine thromboprophylaxis is not recommended for all patients undergoing arthroscopic surgery, but is recommended for those with additional venous thromboembolism risk factors, such as history of DVT or following a prolonged and complicated procedure.<sup>3</sup>

### Impact of Thromboprophylaxis on Risk of Venous Thromboembolism

Thromboprophylaxis	Relative Risk Reduction Compared With Placebo (%)		
	THA	TKA	Hip Fracture Surgery
Low-dose heparin	32-45	33-44	44
Adjusted-dose heparin	74-78		
Low-molecular-weight heparin	70-71	51-52	44
Aspirin	0-26	0-13	29
Recombinant hirudin	67-70		
Warfarin	59-61	23-27	48-50
Elastic stockings	23-25	5-6	
Intermittent pneumatic compression	57-63	56-82	
Foot impulse pump	41		
Fondaparinux*	45	63	62

*Abbreviations: THA=total hip arthroplasty and TKA=total knee arthroplasty.  
\*Odds reduction for venous thromboembolism for fondaparinux is compared with low-molecular-weight heparin.<sup>23</sup>*

Various forms of pharmacological and non-pharmacological thromboprophylaxis have been shown to be effective in reducing the risk of venous thromboembolism in patients undergoing orthopedic surgery.<sup>16</sup> In clinical trials, thromboprophylaxis has been shown to reduce the risk of DVT in patients undergoing THA by between 23% and 78%, with lower but significant risk reductions after TKA or hip fracture surgery (Table 2). Similar results have been obtained in meta-analyses.<sup>18-21</sup> For example, in a meta-analysis of data from approximately 11,000 patients undergoing elective THA, the risk of DVT was reduced by 36%-64%, and that of proximal DVT by 70%-76%, in patients receiving various forms of thromboprophylaxis.<sup>18</sup> In patients undergoing TKA, thromboprophylaxis with low-molecular-weight heparin has been reported to reduce the incidence of DVT by 48%, compared with placebo.<sup>19</sup> Thromboprophylaxis with low-molecular-weight heparin has been shown in another meta-analysis to be significantly more effective than warfarin or aspirin in preventing DVT in patients undergoing TKA.<sup>20</sup> Moreover, Dahl et al<sup>22</sup> reported that discontinuation of thromboprophylaxis with low-molecular-weight heparin in patients undergoing THA one week after surgery allowed a secondary wave of coagulation to occur, which was absent from the group of patients still receiving low-molecular-weight heparin.

The efficacy and safety of thromboprophylaxis using the new anticoagulants fondaparinux and ximelagatran has been compared with low-molecular-weight heparin in patients undergoing major orthopedic surgery. In a meta-analysis of four multicenter, randomized, double-blind trials in patients undergoing elective THA, elective major knee surgery, and hip fracture surgery, a 55.2% risk reduction of venous thromboembolism was observed in the fondaparinux group compared with the enoxaparin group.<sup>23</sup> However, bleeding complications occurred significantly more often in the fondaparinux group. Clinical studies of ximelagatran in major orthopedic surgery patients have reported that, depending on the dose, duration, and timing of administration, the incidence of venous thromboembolism in patients undergoing THA or TKA was 7.9%-31% with ximelagatran compared with 4.6%-28.2% with low-molecular-weight heparin.<sup>24-26</sup> Although ximelagatran was approved for short-term use in major elective orthopedic surgery by the European Union in 2004, the Advisory Committee to the US Food and Drug Administration (FDA) recently rejected an application for its use because of safety concerns regarding liver toxicity.<sup>27,28</sup>

### Risk Factors for Thromboembolism in Orthopedic Surgery Patients

A variety of factors related to the clinical setting and patient influence the risk of venous thromboembolism in orthopedic surgery patients (Table 3).<sup>6,7,9,29,30</sup>

### Procedural or Exposing Surgical Factors

It is well established that compared to general surgery orthopedic surgery is associated with a higher risk of venous thromboembolism.<sup>9</sup> This increased risk can be understood in terms of the so-called Virchow's triad that defines the mechanisms responsible for the development of thrombosis: vessel trauma, hypercoagulability, and stasis.<sup>9,30</sup> Damage to muscle and bone during orthopedic surgery triggers the release of tissue factor and plasminogen activator inhibitor, thereby initiating the coagulation process, while endothelial damage resulting from bone fracture exposes the subendothelium to circulating coagulation factors, resulting in thrombogenesis. Distortion of the femoral vein impairs venous return from the legs, leading to stasis in the lower limbs, which is exacerbated by prolonged immobilization.<sup>9,30</sup>

The type of anesthesia used also can influence thromboembolic risk. In patients undergoing hip fracture surgery, eg, the incidence of venographically documented DVT is approximately twice as high with general anesthesia as with subarachnoid blockade.<sup>30,31</sup>

Clinical-setting-related Risk Factors	Patient-related Risk Factors		
	Clinical	Inherited	Acquired
Type or duration of surgery	Previous venous thromboembolism	Activated protein C resistance	Lupus anticoagulant
Orthopedic surgery	Varicose veins	Deficiencies in: antithrombin, heparin cofactor II, protein C, protein S	Anticardiolipin antibodies
Pelvic or hip fracture	Aged >70 years	Prothrombin mutation	Myeloproliferative disease
Type of anesthesia	Obesity	Hyperhomocysteinemia	Hyperhomocysteinemia
Congestive heart failure	Prolonged bed rest		
Intensive care	Level of hydration		
Multiple trauma	Severe medical illness		
	Infection or sepsis		
	Pregnancy or childbirth		
	Combined oral contraceptives		
	Stroke		
	Myocardial infarction		

### Patient-Related or Predisposing Factors

Clinical factors that increase the risk of venous thromboembolism include a history of previous DVT or varicose veins, age, use of oral contraceptives, pregnancy, and comorbidity; in particular, cancer, myocardial infarction, and stroke are associated with a high risk of venous thromboembolism.<sup>3,30</sup>

In addition to these clinical factors, a number of congenital or acquired molecular factors that result in a hypercoagulable state have been identified (Table 3), and it is estimated that 20%-30% of patients with DVT have such conditions.<sup>7</sup> Inherited risk factors include activated protein C resistance and deficiencies in antithrombin III, protein C, and protein S. The relative impact of these factors on the risk of venous thromboembolism has been investigated in a retrospective family cohort study.<sup>32</sup> Antithrombin III deficiency was associated with a higher risk of venous thromboembolism than other congenital conditions, being associated with a lifetime risk 4.4 times higher than that seen with activated protein C resistance, and 2-3 times higher than that seen with protein C or protein S deficiency. Acquired thrombophilic conditions include lupus anticoagulants, anticardiolipin antibodies, and hyperhomocysteinemia.<sup>30</sup>

Thromboembolic risk factors have a cumulative effect on the overall level of risk and, hence, patients with multiple risk factors are at greatly increased risk.<sup>7</sup> The impact of specific risk factors, individually and in combination, has recently been investigated in a population-based, case-control study in Olmsted County, Minnesota.<sup>29</sup> Fifty-nine percent of cases of first venous thromboembolism occurring over a 15-year period were attributed to hospitalization (with or without surgery) or nursing home residence, while 74% were attributed to eight risk factors (hospitalization or nursing home residence; malignant disease; trauma; congestive heart failure; prior central venous catheter or pacemaker; neurological disease with extremity paresis; prior superficial vein thrombosis; and varicose veins). Similarly, a case-control study in California identified risk factors associated with symptomatic venous thromboembolism following hospital discharge in patients undergoing THA.<sup>33</sup> A body mass index  $\geq 25$  was significantly associated with an increased risk

of venous thromboembolism. Conversely, intermittent pneumatic compression or warfarin use were independent predictors of reduced risk of venous thromboembolism.

## Risk-Assessment Models in Orthopedic Surgery

Risk-assessment models are designed to predict the risk of venous thromboembolism in an individual patient, thus facilitating informed decisions regarding therapy. Risk-assessment models can be used to determine when thromboprophylaxis is required (thus allowing thromboprophylaxis to be targeted to at-risk patients), to guide the choice of therapy, and to identify patients from whom thromboprophylaxis can be safely withheld.<sup>34</sup> To be clinically useful, however, risk-assessment models must satisfy a number of criteria.<sup>34</sup> First, the risk-assessment model should be able to accurately identify all patients at risk of developing DVT if without thromboprophylaxis. Failure to identify patients at risk of DVT, such as young patients undergoing minor surgery who have occult risk factors, could lead to a failure to give thromboprophylaxis and, subsequently, to fatal PE. Second, the model should reliably exclude patients who would be unlikely to develop DVT in the absence of thromboprophylaxis. Third, the risk-assessment model should predict the correct level of risk, allowing thromboprophylaxis to be tailored to the individual patient's needs. Finally, it should be simple to use in routine clinical practice, with minimal need for laboratory investigations or complex calculations.

Risk	Incidence of Calf DVT (%)	Incidence of Proximal DVT (%)	Incidence of Clinical PE (%)	Incidence of Fatal PE (%)	Successful Prevention Strategies
<b>Low</b> Minor surgery in patients aged <40 years, with no additional risk factors	2	0.4	0.2	<0.01	No specific prophylaxis; early and "aggressive" mobilization
<b>Moderate</b> Minor surgery in patients with additional risk factors Surgery in patients aged 40-60 years with no additional risk factors	10-20	2-4	1-2	0.1-0.4	Low-dose unfractionated heparin (every 12 h), LMWH (3400 U daily), graduated compression stockings, or IPC
<b>High</b> Surgery in patients aged >60 years, or age 40-60 with additional risk factors (prior VTE, cancer, molecular hypercoagulability)	20-40	4-8	2-4	0.4-1.0	Low-dose unfractionated heparin (every 8 h), LMWH (>3400 U daily), or IPC
<b>Highest</b> Surgery in patients with multiple risk factors (aged >40 years, cancer, prior VTE) Hip or knee arthroplasty or hip fracture surgery Major trauma or spinal cord injury	40-80	10-20	4-10	0.2-5	LMWH (>3400 U daily), fondaparinux, oral vitamin K antagonists (INR 2-3), or either IPC or graduated compression stockings plus low-dose unfractionated heparin or LMWH

*Abbreviations: ACCP=American College of Chest Physicians, DVT=deep-vein thrombosis, IPC=intermittent pneumatic compression, LMWH=low-molecular-weight heparin, PE=pulmonary embolism, and VTE=venous thromboembolism.*

## Current Risk-Assessment Models in Orthopedic Surgery

Two principal approaches have been used to develop risk-assessment models.<sup>34</sup> The first involved the use of risk-factor indices to assess the level of risk associated with specific risk factors. These models, however, had a number of limitations, including reliance on laboratory investigations, selective inclusion of risk factors, and the use of only small patient populations in validation and development stages. As a result, they have not been widely adopted in clinical practice.<sup>34</sup>

The second approach involved the use of a wide range of risk factors—including those associated with the clinical setting and underlying patient characteristics—to stratify patients into broad risk categories. A number of such risk-assessment models have been developed and applied to orthopedic surgery patients.<sup>2,3,6,7,35-37</sup>

The latest guidelines published by the ACCP stratify patients into 4 risk categories based on risk factors, which are not specifically defined, and the clinical setting.<sup>2</sup> According to these guidelines, the highest risks are seen in patients undergoing THA, TKA, or hip fracture surgery, patients with major trauma or spinal cord injury, and patients with multiple risk factors (aged >40 years, prior venous thromboembolism, or cancer) (Table 4). Specific thromboprophylactic strategies are recommended for patients at moderate risk and above. For patients at highest risk, these include low-molecular-weight heparin, fondaparinux, oral anticoagulants, and either intermittent pneumatic compression or graduated compression stockings with low-molecular-weight heparin or low-dose unfractionated heparin.<sup>2</sup>

The guidelines of the Second Thromboembolic Risk Factors (THRIFT-II) group categorize surgical patients as low, medium, or high risk based on the type of surgery (major or minor), duration of surgery (<30 minutes or >30 minutes), age (<40 years or >40 years),

and a series of defined risk factors, including medical history, clinical features, and blood tests.<sup>35</sup> Total hip or knee arthroplasty are classified as both moderate- and high-risk procedures (Tables 5 and 6). Therapy recommendations emphasize the use of low-molecular-weight heparin, noting that they are more effective than unfractionated heparins, at least as effective as warfarin in THA patients, and more effective than warfarin in TKA patients.<sup>35</sup>

TABLE 5

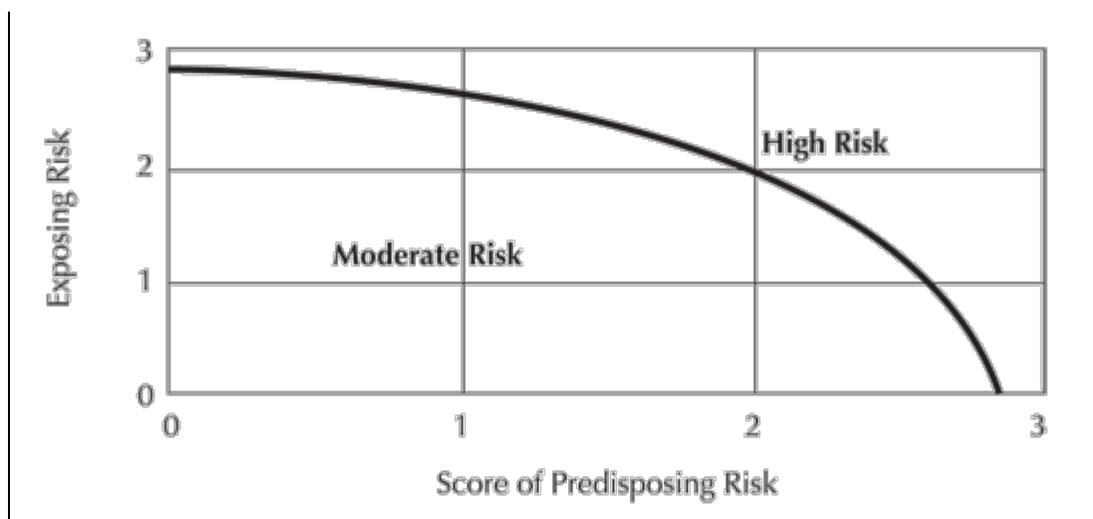
**Classification of Venous Thromboembolism Risk in the Thromboembolic Risk Factor Guidelines<sup>35</sup>**

Risk	Incidence of DVT (%)	Incidence of Proximal DVT (%)	Incidence of Fatal PE (%)
<b>Low</b>			
Minor surgery (<30 minutes)	<10	<1	0.01
Major surgery (>30 minutes), aged <40 years, no other risk factors			
Minor trauma or medical illness			
<b>Moderate</b>			
Major general, urological, gynecological, cardiothoracic, vascular, or neurological surgery, aged >40 years or other risk factors	10-40	1-10	0.1-1
Major medical illness			
Major trauma or burns			
Minor surgery, trauma, or illness in patients with previous DVT, PE, or thrombophilia			
Lower limb paralysis			
<b>High</b>			
Major pelvic or abdominal surgery for cancer	40-80	10-30	1-10
Major surgery, trauma, or illness in patients with previous DVT, PE, or thrombophilia			
Full limb paralysis			
Major limb amputation			
THA and TKA			

*Abbreviations: DVT=deep vein thrombosis, PE=pulmonary embolism, THA=total hip arthroplasty, and TKA=total knee arthroplasty.*

In contrast to the ACCP and THRIFT-II guidelines, in which all surgical patients are considered as one group, the International Consensus Statement on the prevention of venous thromboembolism includes separate classifications for general surgery, gynecological surgery, obstetrics, and medical patients, but no such classification is presented for orthopedic patients.<sup>3</sup> However, the incidences of DVT and fatal PE following THA or TKA in these guidelines are comparable with those presented in the ACCP and THRIFT-II guidelines, and, hence, these procedures are considered to carry a moderate-to-high risk. No specific therapy recommendations are presented.

Each of these risk-assessment models stratifies surgical patients into broad risk categories, but does not consider differences in the risks associated with different types of orthopedic surgery in the individual patient.<sup>6,7</sup> This limitation has been addressed in a further model, which provides a graphic measure of the overall risk in the individual patient.<sup>38</sup> This model rates the risk associated with surgery (the exposing risk) and combines it with the risk associated with various patient-related factors (the predisposing risk). The overall risk of venous thromboembolism can then be read from a plot of exposing risk against predisposing risk (Figure). The exposing risk is rated on a scale of 1 to 3 and takes into account the type of surgery or trauma and the degree of immobilization. Total hip or knee arthroplasty are considered high-risk procedures, whereas arthroscopy is considered a moderate-risk procedure (Figure). The predisposing risk score is calculated from the sum of the scores for a series of individual risk factors, which range from 0.5 to 1.5 (Figure). In contrast to other risk-assessment models, this model identifies orthopedic procedures and trauma as specific risk factors, and attempts to quantify the contribution of individual patient factors to the overall risk. It does not, however, offer therapy recommendations, and its use is currently restricted to orthopedic patients.



### Risk of Venous Thromboembolism After Hospital Discharge

Although the need for thromboprophylaxis in orthopedic surgery patients is widely accepted, the optimal duration of therapy is debatable.<sup>14,39-43</sup> Increasing evidence suggests that extending the duration of thromboprophylaxis beyond the in-hospital period offers important clinical benefits. Specifically, several case-control studies have assessed the incidence of DVT occurring post-discharge. Asymptomatic DVT was reported in approximately 50% of patients.<sup>14,44</sup> Symptoms of DVT occurred 4 to 5 weeks after surgery for THA and TKA, and one day after knee arthroscopy.<sup>45</sup> Moreover, patients undergoing THA or TKA had a higher mortality rate compared with a control population.<sup>46</sup>

### Duration of Venous Thromboembolism Risk After Orthopedic Surgery

The risk of DVT after hip surgery persists for longer than after abdominal surgery,<sup>16</sup> and evidence suggests that the risk may extend for up to several months after surgery.<sup>39</sup> The peak incidence of clinical DVT appears to occur 5 to 10 days after THA or TKA, and hence thromboprophylaxis normally is administered until discharge from the hospital.<sup>39</sup> However, among patients receiving thromboprophylaxis in the hospital, the incidence of venographically confirmed DVT at discharge is 15%-30%, and a further 10%-25% of patients develop asymptomatic DVT in the 3 to 4 weeks after discharge.<sup>47-49</sup> In the recent meta-analysis by Douketis et al,<sup>10</sup> the overall frequency of symptomatic venous thromboembolism within 3 months of surgery in >6000 patients who had undergone THA or TKA and who received low-molecular-weight heparin or warfarin for 7 to 10 days was 3.2%; 1.1% occurred in patients while receiving thromboprophylaxis in the hospital and 2.2% occurred during approximately 80 days after patients stopped thromboprophylaxis and left the hospital.<sup>10</sup> Confirmed fatal PE occurred in 0.1% of patients; 0.04% occurred in-hospital and 0.06% occurred post-discharge. Such findings raise the question of how long thromboprophylaxis should be continued.

TABLE 6

**Classification of Venous Thromboembolism Risk Factors in the Thromboembolic Risk Factor Guidelines<sup>35</sup>**

Patient History	Clinical Signs/Existing Conditions	Blood Tests
Family history or personal past history of DVT	Obesity	Hemoglobin
Age	Varicose veins	Platelets
Obesity	Malignancy	Fibrinogen
Varicose veins	Heart failure	Factor V Leiden mutation
Pregnancy and childbirth	Paralysis	Activated protein C resistance
Estrogen therapy	Immobility	Antithrombin
Thrombophilia (see blood tests)		Protein C
Inflammatory bowel disease		Protein S
Nephrotic syndrome		Antiphospholipid antibody or lupus anticoagulant
Polycythemia		Prothrombin gene mutation
Paraproteinemia		Methylene tetrahydrofolate reductase gene mutation
Paroxysmal nocturnal hemoglobinuria		
Behçet's disease		

*Abbreviation: DVT=deep vein thrombosis.*

Current consensus guidelines recommend thromboprophylaxis with low-molecular-weight heparin, fondaparinux or a vitamin K antagonist for at least 10 days after THA, TKA, or hip fracture surgery.<sup>2,3</sup> In patients undergoing THA or hip fracture surgery, ACCP guidelines recommend extended-duration prophylaxis for 28 to 35 days.<sup>2</sup>

## Clinical Experience With Extended-Duration Thromboprophylaxis

### Efficacy

Currently, orthopedic surgery patients may receive extended-duration thromboprophylaxis with warfarin or with low-molecular-weight heparin. However, issues remain regarding the use of warfarin in this indication. Extended-duration thromboprophylaxis with warfarin resulted in a significant risk reduction of developing venous thromboembolism (0.5% for warfarin versus 9.5% for the control group).<sup>50</sup>

However, Caprini et al<sup>51</sup> showed that despite extended-duration thromboprophylaxis with warfarin, almost 50% of the cases of total vein thrombosis in their study developed after hospital discharge. This was particularly true for patients in whom the International Normalized Ratio (INR) was below the therapeutic range of 2.0-3.0.

Several clinical studies and meta-analyses have shown that extended-duration thromboprophylaxis with low-molecular-weight heparin or unfractionated heparin significantly reduces the incidence of symptomatic DVT in orthopedic surgery patients.<sup>41,42,47-49,52-55</sup> In one such analysis, which included data from 6 randomized controlled trials involving approximately 2000 patients undergoing elective THA, low-molecular-weight heparin thromboprophylaxis for 27 to 35 days reduced the incidence of venographically documented DVT by 59%, and that of proximal or symptomatic DVT by 69% and 64%, respectively, compared with in-hospital thromboprophylaxis followed by out-of-hospital placebo.<sup>42</sup> A further meta-analysis investigated the impact of extended-duration thromboprophylaxis in 3999 patients undergoing THA or TKA.<sup>52</sup> Extending the duration of thromboprophylaxis resulted in a significant 62% reduction in the incidence of symptomatic DVT. Patients undergoing THA showed greater risk reductions than those undergoing TKA (risk reduction 67% versus 26%, respectively), although the reductions achieved were significant in both groups. There also was a significant reduction of 52% in the incidence of asymptomatic, venographically confirmed, DVT in patients undergoing THA or TKA.

### Safety

Concern over increased bleeding risks has been cited as a reason for not using thromboprophylaxis routinely.<sup>2</sup> The data from meta-analyses and individual trials, however, show that extended-duration thromboprophylaxis with low-molecular-weight heparin does not increase the risk of major bleeding.<sup>3,42,43,52</sup> In the analysis described earlier, the incidence of major bleeding was 0.1% in patients receiving extended-duration thromboprophylaxis, compared with 0.3% in placebo-treated or untreated patients.<sup>52</sup> Similarly, in a meta-analysis by Hull et al,<sup>42</sup> only one incidence of major bleeding occurred in a placebo-treated patient. Extended-duration thromboprophylaxis is associated with an increased incidence of minor bleeding, but this is minimal.<sup>42,52</sup>

In the recently published Pentasaccharide in Hip-fracture Surgery (PENTHIFRA)-PLUS study, patients undergoing hip fracture surgery

received either fondaparinux or placebo for 21 days. Extended-duration thromboprophylaxis with fondaparinux resulted in a significant reduction of both symptomatic venous thromboembolism (1.4% versus 35%, respectively) and asymptomatic venous thromboembolism (0.3% versus 2.7%, respectively).

These findings suggest that the routine use of extended-duration thromboprophylaxis is effective and safe. Currently, consensus guidelines recommend the use of extended-duration thromboprophylaxis only in patients at high risk for venous thromboembolism.<sup>2,35</sup> A recent review recommends that extended-duration thromboprophylaxis should be used after major orthopedic surgery in patients with additional risk factors for venous thromboembolism (Table 7).<sup>57</sup> Similarly, the recently updated ACCP guidelines recommend extending thromboprophylaxis to up to 28-35 days following THA or hip fracture surgery.<sup>2</sup>

TABLE 7  
Factors Influencing the Use and Method of Extended Thromboprophylaxis After Major Orthopedic Surgery<sup>57</sup>

Variables	Thromboprophylaxis				
	Fondaparinux	LMWH	Warfarin	Aspirin	None
<b>Risk factors for VTE</b>					
Previous VTE	Strongly favors	Strongly favors	Strongly favors	Weakly favors	Moderately discourages
Cancer (active)	Strongly favors	Strongly favors	Strongly favors	Weakly favors	Moderately discourages
Tamoxifen or estrogen therapy*	Moderately favors	Moderately favors	Moderately favors	Weakly favors	Moderately discourages
Hip versus knee surgery	Weakly favors	Weakly favors	Weakly favors	Weakly favors	Moderately discourages
Known thrombophilia	Moderately favors	Moderately favors	Moderately favors	Weakly favors	Moderately discourages
Slow mobilization or obesity	Weakly favors	Weakly favors	Weakly favors	Weakly favors	
<b>Risk factors for bleeding</b>					
Uncertain surgical site hemostasis	Moderately discourages	Moderately discourages	Moderately discourages	Weakly discourages	Weakly discourages
Previous gastrointestinal bleeding	Weakly discourages	Weakly discourages	Weakly discourages	Weakly discourages	Weakly discourages

*Abbreviations: LMWH=low-molecular-weight heparin and VTE=venous thromboembolism.  
\*Consider withholding tamoxifen or estrogen therapy for 1 month before and after surgery.*

### Cost-effectiveness

It remains to be determined whether the routine use of extended-duration thromboprophylaxis is cost-effective, although it seems likely that the additional costs associated with extended therapy would be acceptable when compared with the costs of treating postoperative venous thromboembolism. In one study, a decision-tree analysis technique was used to compare the costs of extended-duration thromboprophylaxis using low-molecular-weight heparin enoxaparin with those of warfarin in patients undergoing elective THA.<sup>58</sup> The results showed that, when thromboprophylaxis failure and therapy complications were taken into account, enoxaparin maintained a cost-effective advantage over warfarin for 19 to 31 days after discharge from hospital; when the costs of home-care services associated with warfarin were excluded, the duration of cost-effectiveness of enoxaparin was 14 to 17 days. This study suggests that extending thromboprophylaxis with low-molecular-weight heparin for approximately 3 weeks after hospital discharge is cost-effective.

In a second study, decision-tree analysis was used to model the outcomes and costs associated with restricted (2 weeks) or extended-duration (4 weeks) thromboprophylaxis with low-molecular-weight heparin or unfractionated heparin in patients undergoing THA.<sup>59</sup> The overall costs associated with extended-duration thromboprophylaxis were lower than with restricted thromboprophylaxis, while extended-duration low-molecular-weight heparin resulted in an additional gain of quality-adjusted days, compared with unfractionated heparin. These results were confirmed by two additional cost-effectiveness analyses of post-discharge thromboprophylaxis following THA.<sup>60,61</sup> Extended-duration thromboprophylaxis with low-molecular-weight heparin thus was found to be an economically superior therapy over unfractionated heparin: that is, it produced a better clinical outcome at lower overall cost.

The clinical experience with extended-duration thromboprophylaxis in orthopedic surgery patients suggests that this approach is effective for reducing the incidence of venous thromboembolism and is likely to be cost-effective. This would support the routine use of extended-duration thromboprophylaxis in patients at risk for venous thromboembolism. Reliable risk stratification may be central to the effective use of extended-duration thromboprophylaxis, to ensure that clinical benefit and cost-effectiveness are maximized, while minimizing the risk of bleeding complications. However, existing risk-assessment models do not identify patients with additional risk factors,<sup>7</sup> and more research is necessary in this area. Improved risk stratification may make it necessary to revise the recommendations of consensus guidelines to ensure that thromboprophylaxis is used most effectively.<sup>33</sup>

## Conclusion

Despite the availability of effective thromboprophylaxis, the prevention of venous thromboembolism in orthopedic surgery patients remains an important clinical problem. Because the increased risk of venous thromboembolism after orthopedic surgery can persist for several weeks, and discontinuation of anticoagulation therapy can lead to a second wave of thromboembolic complications, extended-duration thromboprophylaxis may be required during this period. Accurate prediction of thromboembolic risk in orthopedic patients also should facilitate the appropriate use of extended-duration thromboprophylaxis, thereby reducing the burden of venous thromboembolism. Improved risk-assessment models therefore are required to identify patients who will benefit from extended-duration thromboprophylaxis.

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