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 or knee arthroplasty. Furthermore, the recently updated ACCP guidelines also recommend extending the duration of thromboprophylaxis for 28-35 days following total hip replacement or hip fracture surgery as the risk of 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.

INTRODUCTION

Venous thromboembolism, including both deep-vein thrombosis and pulmonary embolism, is an important complication of major orthopedic surgery, and is associated with significant morbidity and mortality.[1] Current data suggest that, in the absence of thromboprophylaxis, venographically documented deep-vein thrombosis occurs in approximately 50% of patients undergoing elective hip or knee arthroplasty, and fatal pulmonary embolism may occur in up to 1.7% of patients undergoing knee arthroplasty and up to 2% of those undergoing hip arthroplasty (Table 1). Approximately half of all cases of deep-vein thrombosis after orthopedic surgery involve proximal leg veins.[1,2] Therefore, patients undergoing major orthopedic surgery, such as knee or hip arthroplasty, 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.[2,3]

Despite the existence of national and international guidelines, it is clear that thromboprophylaxis is still inadequately used in orthopedic surgery patients. In one study, for example, only 19% of high-risk patients in non-teaching hospitals and 44% of those in teaching hospitals received adequate thromboprophylaxis.[4] More recently, a review of the medical records of ten hospitals in the USA showed that the percentage of patients receiving appropriate thromboprophylaxis according to the American College of Chest Physicians (ACCP 1995) guidelines was 84% for total hip arthroplasty, 76% for total knee arthroplasty, and 45% for hip fracture surgery.[5] The significance of such under use of therapy is underlined by the fact that pulmonary embolism remains the most common preventable cause of death in hospitalized patients;[6] data suggest that approximately 20,000-30,000 deaths could be prevented each year in the USA alone by the use of appropriate thromboprophylaxis.[6,7]

A number of factors contribute to the inadequate use of thromboprophylaxis in this patient group.[3,6,7] First, the incidence of symptomatic thromboembolic events is relatively low, around 5%, during the perioperative period.[8] As a result, some surgeons may consider deep-vein thrombosis or pulmonary embolism to be rare complications that do not warrant routine thromboprophylaxis.[7] Yet, post-thrombotic complications generally develop over a period of months or years after an acute venous thrombosis, and are usually treated by vascular specialists. Second, concern about potential bleeding complications during anticoagulant therapy may limit the use of thromboprophylaxis.[6,7] However, extensive data from meta-analyses and controlled clinical trials have shown that this risk is largely overestimated: the risk of clinically important bleeding is either not increased or increased only slightly in patients receiving prophylactic doses of low-molecular-weight heparin (LMWH), low dose unfractionated heparin (LDUH), or a vitamin K antagonist (VKA).[3] There is now sufficient evidence to show that appropriately used thromboprophylaxis has a desirable risk/benefit ratio and is cost effective. Therefore, thromboprophylaxis provides an opportunity to both improve patient outcome and to reduce hospital costs.[3]

Improved professional 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.[6,7,9] Despite the use of recommended thromboprophylaxis, however, some high-risk patients (particularly those undergoing total hip or knee arthroplasty) remain at significant risk of deep-vein thrombosis.[9] In a recent meta-analysis, for example, the 3-month incidence of nonfatal, symptomatic venous thromboembolism and fatal pulmonary embolism was 3.2% and 0.1%, respectively, in patients receiving short-term thromboprophylaxis (7-10 days) after hip or knee arthroplasty.[10] Accurate risk assessment is, therefore, 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 incurs increased bleeding risk. Risk assessment

may also 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.[9]

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,[11] 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 regular updating of existing consensus guidelines.

RISK OF VENOUS THROMBOEMBOLISM IN ORTHOPEDIC PATIENTS

As shown in Table 1, the overall incidence of deep-vein thrombosis in patients undergoing hip or knee arthroplasty without thromboprophylaxis is approximately 50%, of which about half are proximal deep-vein thrombi, but the incidence varies according to the surgical procedure. Evidence-based reviews and consensus guidelines suggest that in the absence of thromboprophylaxis the incidence of total and proximal deep-vein thrombosis in patients undergoing total knee arthroplasty ranges from 40-85% and 5-22%, respectively; the corresponding figures for patients undergoing total hip arthroplasty are 42-60% and 16-36%, respectively.[1-3, 11,12] The incidence of asymptomatic pulmonary embolism is less clear, however.[3] In the aforementioned studies, the incidence of total and fatal pulmonary embolism was estimated to be 1.5-10% and 0.1-1.7% in patients undergoing total knee arthroplasty, respectively, and 0.7-30% and 0.1-4% in those undergoing total hip arthroplasty , respectively.[1-3, 11,12] These figures are consistent with the results of a prospective study involving over 6500 patients, in which the overall

incidence of pulmonary embolism 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.[13] In another study, symptomatic deep-vein thrombosis or pulmonary embolism was diagnosed in 2.1% and 2.8% of patients after primary total knee arthroplasty or total hip arthroplasty, respectively.[14] Even more striking is the fact that the events were diagnosed after hospital discharge in 47% and 76% of patients undergoing total knee arthroplasty or total hip arthroplasty, respectively.

In patients undergoing hip fracture surgery, although the incidences of total and proximal deep-vein thrombosis (46-60% and 23-30%, respectively) are comparable with those in patients undergoing hip or knee arthroplasty, the incidence of pulmonary embolism is markedly higher.[1-3,11,12] The overall incidence of pulmonary embolism in patients undergoing hip fracture surgery has been estimated to be between 3% and 24%, while fatal pulmonary embolism has been reported in between 2.5% and 13% of patients.[1-3,11,12]

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 deep-vein thrombosis was present in 18% of patients one week after knee arthroscopy.[15] 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 deep-vein thrombosis or following a prolonged and complicated procedure.[3]

Impact of thromboprophylaxis on risk of venous thromboembolism

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.[16] In clinical trials, thromboprophylaxis has been shown to reduce the risk of deep-vein thrombosis in patients undergoing total hip arthroplasty by between 23% and 78%, with lower but significant risk reductions after knee arthroplasty or hip fracture surgery (Table 2). Similar results have been obtained in meta-analyses.[17-20] For example, in a meta-analysis of data from almost 11,000 patients undergoing elective total hip arthroplasty, the risk of deep-vein thrombosis was reduced by 36-64%, and that of proximal deep-vein thrombosis by 70-76%, in patients receiving various forms of thromboprophylaxis.[17] In patients undergoing total knee arthroplasty, thromboprophylaxis with low-molecular-weight heparin has been reported to reduce the incidence of deep-vein thrombosis by 48%, compared with placebo.[18] Thromboprophylaxis with low-molecular-weight heparin has been shown in another meta-analysis to be significantly more effective than warfarin or aspirin in preventing deep-vein thrombosis in patients undergoing total knee arthroplasty.[19] Moreover, Dahl et al showed that discontinuation of thromboprophylaxis with low-molecular-weight heparins in patients undergoing total hip arthroplasty 1 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.[21]

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 hip arthroplasty, 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.[22] 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 total hip arthroplasty or total knee

arthroplasty was 7.9-31% with ximelagatran compared with 4.6-28.2% with low-molecular-weight heparin.[23-25] 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, major bleeding and myocardial infarction as well as doubts about the manufacturer's plans to monitor and manage liver complications[26,27].

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).[6,7,9,28,29]

Procedural or exposing surgical factors. It is well established that orthopedic surgery is associated with a higher risk of venous thromboembolism than is general surgery.[9] 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.[9,29] 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.[9,29]

The type of anesthesia used can also influence thromboembolic risk. In patients undergoing hip fracture surgery, for example, the incidence of venographically documented deep-vein thrombosis is approximately twice as high with general anesthesia as with subarachnoid blockade. [29,30]

Patient-related or predisposing factors. Clinical factors that increase the risk of venous thromboembolism include a history of previous deep-vein thrombosis 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.[3,29]

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 deep-vein thrombosis have such conditions.[7] 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.[31] 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.[29]

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.[7] 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.[28] It was found that 59% of cases of first venous thromboembolism occurring over a 15-year period could be attributed to hospitalization (with or without surgery) or nursing home residence, while 74% could be 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 was

carried out to identify risk factors associated with symptomatic venous thromboembolism following hospital discharge in patients undergoing total hip arthroplasty.[32] A body mass index of ≥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.[33] To be clinically useful, however, risk-assessment models must satisfy a number of criteria.[33] First, the risk-assessment model should be able to accurately identify all patients at risk of developing deep-vein thrombosis if without thromboprophylaxis. Failure to identify patients at risk of deep-vein thrombosis, such as young patients undergoing minor surgery who have occult risk factors, could lead to a failure to give thromboprophylaxis and, subsequently, to fatal pulmonary embolism. Second, the model should reliably exclude patients who would be unlikely to develop deep-vein thrombosis 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.

Current risk-assessment models in orthopedic surgery

Two principal approaches have been used to develop risk-assessment models.[33] 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.[33]

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.[2,3,6,,7,34-36]

The latest guidelines published by the ACCP stratify patients into 4 risk categories on the basis of risk factors (which are not specifically defined) and the clinical setting.[3] According to these guidelines, the highest risks are seen in patients undergoing hip or knee arthroplasty or hip fracture surgery, together with patients with major trauma or spinal cord injury, and patients with multiple risk factors (over 40 years of age, 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 heparins, fondaparinux, oral anticoagulants, and either intermittent pneumatic compression or graduated compression stockings with low-molecular-weight heparin or low-dose unfractionated heparin.[3]

The guidelines of the Second Thromboembolic Risk Factors (THRIFT-II) group categorize surgical patients as low, medium, or high risk on the basis of 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.[34] Hip or knee arthroplasty are classed as both moderate-risk and high-risk procedures (Table 5). Therapy recommendations emphasize the use of low-molecular-weight heparins, noting that they are more effective than unfractionated heparins, at least as effective as warfarin in hip arthroplasty patients, and more effective than warfarin in knee arthroplasty patients.[34]

In contrast to the ACCP and THRIFT II guidelines, in which all surgical patients are considered as 1 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.[2] However, the incidences of deep-vein thrombosis and fatal pulmonary embolism following total hip or knee arthroplasty 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 forms of orthopedic surgery in the individual patient.[6,7] This limitation has been addressed in a further model, which provides a graphic measure of the overall risk in the individual patient.[37] 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 1). The exposing risk is rated on a scale of 1-3 and takes into account the type of surgery or trauma and the degree of immobilization. Hip or knee arthroplasty are considered high-risk procedures, whereas arthroscopy is considered a moderate-risk procedure (Figure 1). 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 1). 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 remains the subject of much debate.[14,38-42] There is increasing evidence 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 deep-vein thrombosis occurring post-discharge. Asymptomatic deep-vein thrombosis was reported in about 50% of patients.[14,43] Symptoms of deep-vein thrombosis occurred 4-5 weeks after surgery for total hip arthroplasty and total knee arthroplasty, and 1 day after knee arthroscopy.[44] Moreover, patients undergoing total hip arthroplasty or total knee arthroplasty had a higher mortality rate compared with a control population.[45]

Duration of venous thromboembolism risk after orthopedic surgery

The risk of deep-vein thrombosis after hip surgery persists for longer than after abdominal surgery,[16] and there is evidence that the risk may extend for up to several months after surgery.[38] The peak incidence of clinical deep-vein thrombosis appears to occur 5-10 days after hip or knee replacement surgery, and hence thromboprophylaxis is normally administered until discharge from hospital.[38] However, even among patients receiving thromboprophylaxis in hospital, the incidence of venographically confirmed deep-vein thrombosis at discharge is 15-30%, and a further 10-25% of patients develop asymptomatic deep-vein thrombosis in the 3-4 weeks after discharge.[46-48] In the

recent meta-analysis by Douketis et al, the overall frequency of symptomatic venous thromboembolism within 3 months of surgery in over 6000 patients who had undergone total hip arthroplasty or total knee arthroplasty and who received low-molecular-weight heparin or warfarin for 7-10 days was 3.2%; 1.1% occurred in patients while receiving thromboprophylaxis in hospital and 2.2% occurred during about 80 days after patients stopped thromboprophylaxis and left hospital.[10] Confirmed fatal pulmonary embolism 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.

Current consensus guidelines recommend thromboprophylaxis with low-molecular-weight heparin, fondaparinux or a vitamin K antagonist for at least 10 days after hip or knee arthroplasty or hip fracture surgery.[2,3] In patients undergoing total hip arthroplasty or hip fracture surgery, ACCP guidelines recommend extended-duration prophylaxis for 28-35 days.[3]

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).[49] However, Caprini et al. showed that despite extended-duration thromboprophylaxis with warfarin, almost half of the cases of total vein thrombosis in their study developed after hospital discharge.[50] 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 deep-vein thrombosis in orthopedic surgery patients.[40,41,46-48,51-54] In one such analysis, which included data from 6 randomized controlled trials involving a total of approximately 2000 patients undergoing elective hip arthroplasty, low-molecular-weight heparin thromboprophylaxis for 27-35 days reduced the incidence of venographically documented deep-vein thrombosis by 59%, and that of proximal or symptomatic deep-vein thrombosis by 69% and 64%, respectively, compared with in-hospital thromboprophylaxis followed by out-of-hospital placebo.[41] A further meta-analysis investigated the impact of extended-duration thromboprophylaxis in 3999 patients undergoing total hip or knee arthroplasty.[51] Extending the duration of thromboprophylaxis resulted in a significant, 62% reduction in the incidence of symptomatic deep-vein thrombosis. Patients undergoing total hip arthroplasty showed greater risk reductions than those undergoing total knee arthroplasty (risk reduction 67% versus 26%, respectively), although the reductions achieved were significant in both groups. There was also a significant reduction of 52% in the incidence of asymptomatic, venographically confirmed, deep-vein thrombosis in patients undergoing hip or knee arthroplasty.

Safety. Concern over increased bleeding risks has been cited as a reason for not using thromboprophylaxis routinely.[3] 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.[3,41,42,51] In the analysis described earlier, for example, the incidence of major bleeding was 0.1% in patients receiving extended-duration thromboprophylaxis, compared with 0.3% in placebo-treated or untreated patients.[51] Similarly, in the meta-analysis by Hull et al, there was only one incidence of major bleeding, which occurred in a placebo-treated patient.[41]

Extended-duration thromboprophylaxis is associated with an increased incidence of minor bleeding, but this is slight. [41,51]

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.[53] Extended-duration thromboprophylaxis with fondaparinux resulted in a significant reduction of both symptomatic venous thromboembolism (1.4% versus 35.0%, 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. Such therapy could prevent many more cases of deep-vein thrombosis after orthopedic surgery than is currently the case. At present, however, consensus guidelines recommend the use of extended-duration thromboprophylaxis only in patients at high risk of venous thromboembolism.[3,34]. 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 6).[56] Similarly, the recently updated ACCP guidelines recommend extending thromboprophylaxis to up to 28-35 days following hip replacement or hip fracture surgery.[3]

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 set against 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 the low-molecular-weight heparin enoxaparin with those of warfarin in patients undergoing elective hip arthroplasty.[57] The results

showed that, when thromboprophylaxis failure and therapy complications were taken into account, enoxaparin maintained a cost-effective advantage over warfarin for 19-31 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 14-17 days. This study suggests, therefore, 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 total hip arthroplasty.[58] 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 hip arthroplasty surgery.[59,60] Extended-duration thromboprophylaxis with low-molecular-weight heparin was thus found to be an economically superior therapy over unfractionated heparin: that is, it produced a better clinical outcome at lower cost.

In summary, 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 of 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. At present, however, existing risk-assessment models do not identify patients with additional risk factors,[7] 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.[33]

CONCLUSIONS

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 should also facilitate the appropriate use of extended-duration thromboprophylaxis, thereby reducing the burden of venous thromboembolism. Improved risk-assessment models are therefore required to identify patients who will benefit from extended-duration thromboprophylaxis.

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TABLE 1. Incidence of venous thromboembolism in major orthopedic surgery patients not receiving thromboprophylaxis*.[3] [Permission requested]

Type of surgery	Total DVT	Proximal DVT	Total PE	Fatal PE
Hip arthroplasty	42–57%	18–36%	0.9–28%	0.1–2.0%
Knee arthroplasty	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 and PE=pulmonary embolism.

* DVT rates are based on mandatory venography in prospective clinical trials published since 1980 in which patients received either placebo or no prophylaxis. PE rates were derived from prospective studies that may have included prophylaxis.

TABLE 2. Reductions in risk of deep-vein thrombosis in orthopedic surgery patients receiving various forms of thromboprophylaxis.[16,61] [Permission requested]

Type of surgery and thromboprophylaxis	Relative risk reduction compared with placebo, (%)
Total hip arthroplasty*	
Low-dose heparin	32–45
Adjusted-dose heparin	74–78
Low-molecular-weight heparin	70–71
Aspirin	0–26
Recombinant hirudin	67–70
Warfarin	59–61
Elastic stockings	23–25
Intermittent pneumatic compression	57–63
Foot impulse pump	41
Fondaparinux*	45
Total knee arthroplasty*	
Low-dose heparin	33–44
Low-molecular-weight heparin	51–52
Aspirin	0–13
Warfarin	23–27
Elastic compression stockings	5-6
Intermittent pneumatic compression	56-82
Fondaparinux*	63
Hip fracture surgery*	
Low-dose heparin	44

Low-molecular-weight heparin	44
Warfarin	48–50
Aspirin	29
Fondaparinux*	62

* Odds reduction for venous thromboembolism for fondaparinux is compared with low-molecular-weight heparin (from Turpie et al [2002]).[22]

TABLE 3. Risk factors for venous thromboembolism in orthopedic surgery patients.[6] [Permission requested]

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:	Anticardiolipin antibodies
Pelvic or hip fracture	Age >70 years	antithrombin	Myeloproliferative disease
Type of anesthesia	Obesity	heparin cofactor II	Hyperhomocysteinemia
Congestive heart failure	Prolonged bed rest	Protein C	
Intensive care	Level of hydration	Protein S	
Multiple trauma	Severe medical illness	Prothrombin mutation	
	Infection or sepsis	Hyperhomocysteinemia	
	Pregnancy or childbirth		
	Combined oral contraceptives		
	Stroke		
	Myocardial infarction		

TABLE 4. Incidence of thromboembolism risk according to the ACCP guidelines.[3] [Permission requested]

	Incidence of calf DVT (%)	Incidence of proximal DVT (%)	Incidence of clinical PE (%)	Incidence of fatal PE (%)	Successful prevention strategies
Low risk 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
Moderate risk 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 (q12h), LMWH (≤3400 U daily), graduated compression stockings, or IPC
High risk 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 (q8h), LMWH (>3400 U daily), or IPC

(Table 4 cont.)

Highest risk Surgery in patients with multiple risk factors (age >40	40-80	10-20	4-10	0.2-5	LMWH (>3400 U daily), fondaparinux, oral vitamin K antagonists (INR 2-3), or

years, cancer, prior VTE)	either IPC or graduated compression
Hip or knee arthroplasty or hip fracture surgery	stockings plus low-dose unfractionated
Major trauma or spinal cord injury	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.

TABLE 5. Classification of venous thromboembolism risk (a) and risk factors (b) in the THRIFT II guidelines.[34] [Permission requested]

a

	Incidence of DVT (%)	Incidence of proximal DVT (%)	Incidence of fatal PE (%)
Low risk	<10	<1	0.01
Minor surgery (<30 minutes)			
Major surgery (>30 minutes), aged <40 years, no other risk factors			
Minor trauma or medical illness			
Moderate risk	10-40	1-10	0.1-1
Major general, urological, gynecological, cardiothoracic, vascular, or neurological surgery, aged >40 years or other risk factors			
Major medical illness			
Major trauma or burns			
Minor surgery, trauma, or illness in patients with previous DVT, PE, or thrombophilia			
Lower limb paralysis			

(a cont.)

High risk	40-80	10-30	1-10
Major pelvic or abdominal surgery for cancer			
Major surgery, trauma, or illness in patients with previous DVT, PE, or thrombophilia			
Full limb paralysis			
Major limb amputation			
Hip and knee replacement			

Abbreviations: DVT=deep-vein thrombosis, PE=pulmonary embolism, THRIFT=Thromboembolic Risk Factors.

b

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		
Paraproteinemia		Prothrombin gene mutation
Paroxysmal nocturnal hemoglobinuria		Methylene tetrahydrofolate reductase gene mutation
Behçet's disease		

Abbreviations: DVT=deep-vein thrombosis.

TABLE 6. Factors influencing the use and method of extended thromboprophylaxis after major orthopedic surgery.[56] [Permission requested]

Variables	Method of thromboprophylaxis				
	Fondaparinux	LMWH	Warfarin	Aspirin	None
Risk factors for VTE					
Previous VTE	+++	+++	+++	+	−−
Cancer (active)	+++	+++	+++	+	−−
Tamoxifen or estrogen therapy*	++	++	++	+	−−
Hip versus knee surgery	+	+	+	+	
Known thrombophilia	++	++	++	+	−−
Slow mobilization or obesity	+	+	+	+	
Risk factors for bleeding					
Uncertain surgical site hemostasis	−−	−−	−−	−	−
Previous gastrointestinal bleeding	−	−	−	−	−

Abbreviations: LMWH=low-molecular-weight heparin and VTE=venous thromboembolism.

Key: +++ =strongly favors, ++ =moderately favors, + =weakly favors, − =weakly discourages, −− =moderately discourages.

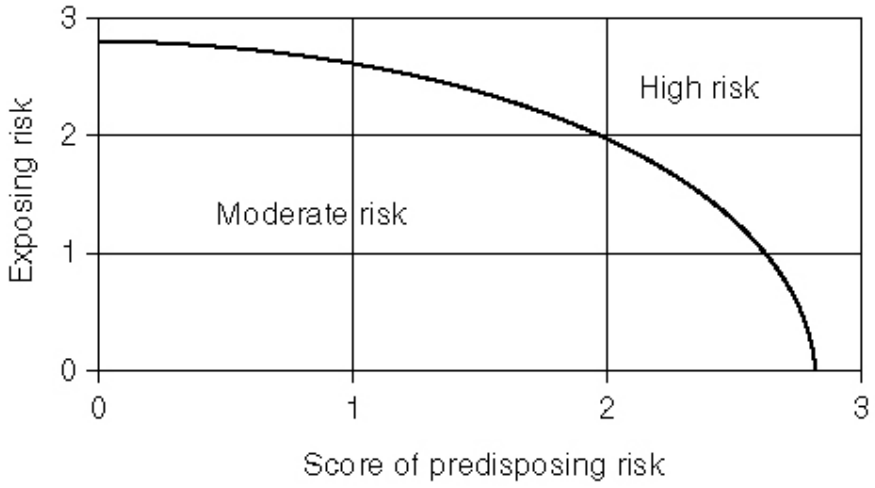
*Consider withholding tamoxifen or estrogen therapy for 1 month before and after surgery.

FIGURE LEGENDS

FIGURE 1. The risk-assessment model for venous thromboembolism designed by Haas.[6,36]

[Permission requested]

FIGURE 1


3
2
1
0
Exposing risk
High risk
Moderate risk
0
1
2
3
Score of predisposing risk