CHAPTER 4

Thromboprophylaxis in Orthopaedic Surgery

ANTHONY G. BEETON/ANDRÉ P. BOEZAART

INTRODUCTION

Venous thromboembolism (VTE) encompasses acute thrombotic events such as symptomatic and asymptomatic deep venous thrombosis (DVT), pulmonary embolism (PE), and chronic sequelae such as recurrent VTE, postthrombotic syndrome (PTS), and the manifestations of chronic pulmonary thromboembolic disease.\(^1,2\) Certain major orthopaedic surgical procedures such as total hip arthroplasty (THA), total knee arthroplasty (TKA), hip fracture surgery (HFS), and major pelvic surgery represent situations with a particular risk for VTE.\(^1,3\)

NORMAL HEMOSTASIS

Hemostasis is a complex process designed to defend and preserve the integrity and patency of the vascular system. It involves interactions between the vascular endothelium, platelets, clotting factors, and the fibrinolytic system.\(^4,5\)

The endothelium has an array of functions in hemostasis. It releases endothelin in response to injury, provoking intense vasoconstriction. This reduces bleeding and results in sustained contact between the damaged endothelium, platelets, and coagulation factors, thereby promoting clotting. It also modulates the degree of coagulation, producing not only procoagulant agents such as tissue factor (TF) and von Willebrand factor (vWF) but also anticoagulants (nitric oxide, endothelium-derived relaxant factor, thrombomodulin, and tissue factor pathway inhibitor) and fibrinolytic system components (tissue plasminogen activator).\(^5\)

Platelets are responsible for the formation of the initial plug at the site of vascular injury. They have surface receptors for interaction with other platelets, von Willebrand factor (vWF), fibrinogen, and collagen and form the nidus for formation of the primary clot. They also produce the phospholipids required for normal coagulation.\(^5\)

The coagulation pathway is designed to produce thrombin (factor IIa), the key enzyme in hemostasis.\(^6\) Thrombin catalyzes the conversion of soluble fibrinogen to fibrin, which is the major component of the clot.\(^7\) Fibrin then forms cross-links to produce a stable clot.\(^5\) These steps represent the common coagulation pathway. Thrombin is formed via the intrinsic and extrinsic coagulation pathways.\(^8\) The intrinsic pathway is the major source of thrombin generation and is activated by exposure of blood to subendothelial connective tissue. It produces a massive, focused burst of thrombin synthesis.\(^5,7,8\) The smaller extrinsic pathway produces a smaller amount of thrombin in response to contact between blood and TF. Its action is more rapid than that of the intrinsic pathway and serves to augment it.\(^7\)

The extent of clotting is controlled by circulating regulators of coagulation and by the fibrinolytic system. Several activators convert plasminogen to plasmin, the major fibrinolytic protein.\(^5\) Antithrombin (AT) is the major circulating inhibitor of clotting factors. It forms complexes with these factors, notably factor Xa and thrombin, allowing rapid hepatic clearance. The activity of AT is accelerated 5000 to 10,000-fold by heparin.\(^5,7\)
Other circulating anticoagulants include tissue factor pathway inhibitor (TFPI) and proteins C and S. The last mentioned serves mainly as a cofactor for protein C. Proteins C and S strongly inhibit or inactivate several coagulation factors, accelerating their normal rate of inactivation up to 20,000-fold. TFPI may mediate some of the antithrombotic effects of unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) as it is released from the vascular endothelium in response to therapeutic doses of these agents. Thrombomodulin is an endothelial receptor that binds circulating thrombin and prevents clot formation in undamaged vessels.

► RISK FACTORS FOR VENOUS THROMBOEMBOLISM

The risk for VTE is a composite of various demographic and comorbid factors that make up the predisposing risk and factors related to the surgical procedure that form the exposing risk. The major risk factors are tabulated below. These are additive, although some (e.g., age, malignancy, and previous VTE) may carry more weight than others. Patients may therefore be classified into risk categories ranging from lowest to highest risk. The patients at greatest risk for VTE are those who undergo major orthopaedic surgery of the lower limbs and victims of major trauma or acute spinal cord injury. Risk stratification for other orthopaedic patients depends largely on age, duration of surgery, and the presence of additional risk factors (Table 4-1).

Predisposition to VTE is based on disturbances in one or more components of Virchow's triad: the vascular endothelium, blood coagulability, and blood flow (stasis). Major hip and knee surgeries (THA, TKA, and HSF) cause significant and sustained alterations in all of these components.

The vascular endothelium has been shown by intraoperative venography to be damaged or disrupted by direct surgical trauma. In addition, twisting and folding of the common femoral vein during hip dislocation produces distention and breakage of endothelial intercellular bridges and exposure of collagen and tissue factors. Retractors (e.g., the posterior tibial retractor in TKA) may have similar effects. The heat generated by the polymerization of methyl methacrylate also causes endothelial injury (see Chap. 33). The consequences of these injuries are platelet adherence and aggregation, initiation of coagulation, and decreased endothelial function.

Hypercoagulability, as evidenced by circulating markers of thrombosis, commences at the time of femoral canal reaming, peaks at insertion of the cemented stem, and continues for up to 5 weeks postoperatively. Noncemented prostheses appear to be less thrombogenic. Hypercoagulability results from bone marrow destruction and the release of TF. Bone cement increases thrombin activity. Fibrinolytic failure contributes to the risk of thrombosis.

Intraoperative venography has also shown a significant reduction in venous blood flow and stasis in lower limb orthopaedic surgery. This is related to venous obstruction in all cases and to the use of a tourniquet in TKA (see Chap. 11). The immobilization and bed rest associated with these procedures exacerbates stasis. Reduced venous flow affects both the operated and the contralateral limb. Reduced venous blood flow may last for up to 6 weeks after surgery. In TKA, the majority of DVT starts in the calf veins but may propagate proximally in 15 percent of cases. In hip surgery and trauma, DVT may arise primarily in

► TABLE 4-1. RISK FACTORS FOR VENOUS THROMBOEMBOLISM (VTE)

<table>
<thead>
<tr>
<th>Predisposing Risk Factors</th>
<th>Exposing Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Nature of surgery (pelvic and lower limb surgery, cancer surgery, abdominal surgery)</td>
</tr>
<tr>
<td>Prolonged immobility</td>
<td>Duration of surgery</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>Type of anesthesia</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Degree of immobilization</td>
</tr>
<tr>
<td>Obesity</td>
<td>Presence of infection</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>Trauma to spine, pelvis and lower limbs</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td></td>
</tr>
<tr>
<td>Thrombophilic disorders</td>
<td></td>
</tr>
<tr>
<td>Others (pregnancy, hormone replacement therapy, nephrotic syndrome, inflammatory bowel disease, psychotropic drugs, prolonged travel)</td>
<td></td>
</tr>
</tbody>
</table>

VTE = venous thromboembolism.
Sources: Adapted from Geerts et al., Offord and Perry, Samama et al., and Geerts et al.
the proximal veins.\textsuperscript{15} Pulmonary embolism is usually preceded by proximal DVT, the majority of which is clinically silent.\textsuperscript{8,16} It is impossible to predict which distal thrombi may progress to pulmonary embolism.\textsuperscript{17} Therefore, any venographic DVT is accepted as a valid surrogate measure of potentially symptomatic VTE.\textsuperscript{12,15,17}

\section*{INCIDENCE AND IMPACT OF VTE IN ORTHOPAEDIC SURGERY}

Symptomatic DVT and PE represent a small fraction of the total incidence of venographically confirmed VTE. The vast majority of VTE events are clinically silent.\textsuperscript{5,15,18} It is estimated that for every 100 silent cases of DVT, there are 10 clinically detected DVTs and one fatal PE.\textsuperscript{1,15} Bilateral venography has shown that between 7 to 14 days after operation, 41 to 85 percent of patients who undergo lower limb arthroplasty and HFS develop VTE in the absence of thromboprophylaxis.\textsuperscript{1,8} A substantial proportion of VTE (20 to 87 percent) presents during the second and subsequent postoperative weeks, much of it after hospital discharge.\textsuperscript{8,19} Major lower limb orthopaedic surgery is not a homogeneous entity, and differences exist between the procedures in terms of the incidence, distribution, and onset time of VTE events (Table 4-2).\textsuperscript{16}

Following major orthopaedic surgery, VTE is usually silent, but it may present as acute DVT or PE or as a delayed PTS or a recurrent VTE.\textsuperscript{20–22} The use of virtually any thromboprophylactic protocol reduces the risk of VTE by half or more.\textsuperscript{3,15} With the possible exception of dextran infusion (which reduces PE selectively), the reduction is in all components of VTE. Proximal DVT is more likely to be clinically apparent than distal DVT and is also more likely to produce PE. Only 5 to 20 percent of total thrombotic events are, however, clinically apparent.\textsuperscript{23,24} It is therefore clear that the majority of radiologically demonstrated venous thrombosis resolves spontaneously.

\begin{table}[ht]
\centering
\caption{Epidemiology of Venous Thromboembolism Without Prophylaxis Since 1980}
\begin{tabular}{lccc}
 & THA & TKA & HFS \\
\hline
Total DVT (%) & 42–57 & 41–85 & 46–60 \\
Proximal DVT (%) & 18–36 & 5–22 & 23–30 \\
Contralateral DVT (%) & 20 & 14 & \\
PE (%) & 0.9–28 & 1.5–10 & 3–11 \\
Fatal PE (%) & 0.1–2 & 0.1–1.7 & 2.5–7.5 \\
Mean time to VTE (days) & 17 & 7 & 17 \\
\end{tabular}
\end{table}

DVT = deep venous thrombosis; HFS = hip fracture surgery; PE = pulmonary embolism; THA = total hip arthroplasty; TKA = total knee arthroplasty; VTE = venous thromboembolism.

In major orthopaedic surgery, only 20 percent of fatal thrombotic events are suspected before death\textsuperscript{24} and only 12 percent of patients present with clinically apparent DVT before the onset of pulmonary embolism.\textsuperscript{11}

There has been a substantial reduction in the incidence of clinically apparent VTE associated with major orthopaedic surgery in the last 30 years.\textsuperscript{5,12} This is attributable only partly to the use of thromboprophylaxis.\textsuperscript{12} Improvements in surgical technique, general perioperative care, mobilization, analgesia, anesthetic technique, and duration of bed rest/hospitalization have also contributed.\textsuperscript{5,11} This has led to the perception among some orthopaedic surgeons that VTE (particularly fatal PE) is an overemphasized problem and that routine prophylaxis is not indicated. This perception is enhanced by the clinically silent nature of the majority of VTE cases and by the fact that many occur after discharge and frequently present to other specialties.\textsuperscript{8,11,12,25,26}

Venous thrombosis, however, remains a massive problem in major orthopaedic surgery. It is the most common complication of TKA and the likeliest cause of readmission.\textsuperscript{4} It is the second most frequent cause of death associated with THA (causing 18 percent of deaths)\textsuperscript{5,11,12} and ranks third or fourth in HFS (14 percent).\textsuperscript{3,4,11} In 1990, there were an estimated 1.7 million hip fracture procedures worldwide, resulting in about 17,000 deaths due to VTE.\textsuperscript{11} In addition, it is likely that failure to detect VTE during autopsy may cause underestimation of its role as a cause of death.\textsuperscript{11,24} In major orthopaedic surgery, the occurrence of a DVT increases the risk of death 2.5-fold, while PE produces a 20-fold rise.\textsuperscript{7} It is expected that HFS will increase to 6 million worldwide by 2050,\textsuperscript{11} while THA is projected to increase by 25 to 50 percent by 2020 and TKA by 30 percent by 2030.\textsuperscript{2,6,12} At the same time, the population undergoing these procedures is aging. The median age for THA rose by 2 years between 1996 and 2001, and that for TKA by 1 year.\textsuperscript{26} Patients' increasing age along with their likelihood of having more comorbid diseases will increase the risk of VTE in the future.\textsuperscript{4,20}

Venous thrombosis is also responsible for a substantial amount of morbidity.\textsuperscript{5} Recurrent VTE occurs in 20 percent of patients within the 2 years after initial presentation and in 30 percent within 10 years.\textsuperscript{38} Chronic lower limb venous insufficiency follows in 50 to 60 percent of cases of symptomatic proximal DVT and 30 percent of symptomatic calf DVT.\textsuperscript{20} Postthrombotic syndrome (PTS) has an incidence of 8.5 percent 1 year after DVT, rising to 24.1 percent at 20 years (and 36.1 percent after proximal DVT).\textsuperscript{30} Venous ulcers complicate 3.7 percent of DVT by 2020 and TKA by 30 percent by 2030.\textsuperscript{2,6,12} At the same time, the population undergoing these procedures is aging. The median age for THA rose by 2 years between 1996 and 2001, and that for TKA by 1 year.\textsuperscript{26} Patients' increasing age along with their likelihood of having more comorbid diseases will increase the risk of VTE in the future.\textsuperscript{4,20}

The economic impact of VTE is enormous. It is estimated that VTE costs the U.S. health care system $3.2 billion per year.\textsuperscript{30} The impact of VTE on various aspects of health economics is summarized in Table 4-3.
OPTIONS FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM

There is ample evidence that routine prophylaxis during hospitalization is more effective than screening and treatment in this group of patients.\(^4,21,30,32\) It is unclear at present what the cost-benefit ratio is of long-term postdischarge prophylaxis. Evidence for efficacy of long-term prophylaxis (4 weeks) is, however, abundant.\(^21,33\) In view of the high incidence of venous thrombosis in major orthopaedic surgery, a thromboprophylactic strategy is mandatory.\(^16\) This strategy may be nonpharmacologic or pharmacologic or, ideally, may combine both modalities. In general, prophylaxis has a lower success rate in knee arthroplasty than in hip surgery, possibly because many of the thrombi formed are small and distal.\(^3,14,16\)

Nonpharmacologic methods include improved surgical technique (noncemented prostheses, pulsed lavage, minimally invasive surgery, limited use of tourniquet); anesthetic interventions (neuraxial anesthesia, optimal analgesia for early mobilization); autologous blood donation and transfusion; and physical measures (elevation of the foot of the bed, active and passive ankle exercises, early mobilization).\(^1,4,13\) Mechanical methods are graded elastic stockings, intermittent pneumatic calf compression, sequential compression detection devices, and pneumatic plantar plexus compression.\(^1,4,14\) Anesthetic interventions are discussed further in a subsequent section. All of the listed nonpharmacologic methods have been shown to reduce venous thrombosis under specific circumstances, but it is questionable whether any or combination of them provide adequate prophylaxis in high-risk orthopaedic surgery.\(^1,5,12\) They should rather be seen as adjuvant to pharmacologic prophylaxis except when anticoagulants are contraindi- cated (e.g., for excessive bleeding risk).\(^1,5\) Mechanical methods do not cause increased bleeding and are therefore considered to be safe.\(^1\) They may be limited by high acquisition cost, and compliance tends to be incomplete owing to their discomfort. It is not possible to perform properly “blinded” trials to determine their true efficacy, and concerns have been expressed about observer bias.\(^1,5,12\)

Graded elastic stockings have a pressure gradient decreasing from 15 to 18 mmHg at the foot to 5 mmHg at the proximal thigh. They increase peak femoral venous blood flow velocity by 50 percent and reduce stasis. They have no impact on de novo proximal DVT formation in hip surgery and consequently no protective effect against pulmonary embolism. Their cost-effectiveness has not been studied.\(^1,4\)

Intermittent pneumatic compression (IPC), sequential compression detection (SCD) devices, and pneumatic plantar plexus compression increase the velocity of venous blood flow and stimulate fibrinolysis.\(^1,4,14\) They decrease the DVT risk by 20 to 60 percent but have little impact on proximal DVT. They appear to be most effective in knee arthroplasty, but less so than anticoagulants.\(^1,4\)

Dextran infusions are effective in preventing fatal PE in general surgical patients.\(^34\) Dextran enhances blood flow characteristics, decreases platelet adhesion to the endothelium, and increases the lysability of fibrin clots. Its utility in major orthopaedic surgery is unknown. Drawbacks include bleeding, anaphylactic reactions, and cost.\(^1,34\)

Aspirin is not a first-line drug in prophylaxis against venous thrombosis.\(^1,30\) It may protect against fatal pulmonary embolism and postoperative cardiovascular mortality but is less effective than first-line agents for VTE prevention.\(^1,35\) In addition, it poses a high risk of bleeding and gastrointestinal side effects.\(^5,35\)

Except where the bleeding risk is prohibitive, pharmacologic prophylaxis is the cornerstone of the prevention of venous thrombosis in high-risk orthopaedic patients.\(^1,8\) Specific agents are considered in the following section, but certain general rules apply:

1. Each major orthopaedic procedure has unique patient demographics, consequent comorbidities, and balance of thrombotic and bleeding risk. Data from one case are not necessarily applicable to another.\(^2\)

2. Comparison of agents within and between pharmacologic groups is rendered difficult by variations in kinetics as well as recommended dosages and regimens, particularly the time between drug administration and surgery and speed of onset of anticoagulant effect.\(^3,25,36\) Rapid-onset drugs

---

**TABLE 4-3. IMPACT OF VENOUS THROMBOEMBOLISM ON HEALTH ECONOMICS IN MAJOR ORTHOPAEDIC SURGERY**

<table>
<thead>
<tr>
<th></th>
<th>Mean Hospital Stay (Days)</th>
<th>Mean ICU Stay (Days)</th>
<th>Total Inpatient Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No VTE</td>
<td>5.4</td>
<td>0.2</td>
<td>9,345</td>
</tr>
<tr>
<td>DVT</td>
<td>11.5</td>
<td>1.7</td>
<td>17,114</td>
</tr>
<tr>
<td>PE</td>
<td>12.4</td>
<td>2.7</td>
<td>18,521</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Sources: Adapted from Paiement,\(^4\) Agnelli et al.,\(^19\) and Anderson et al.\(^27\)
PHARMACOLOGY OF ANTIHEMORRHAGIC MEDICATIONS

Major orthopaedic surgery is an ideal model for the assessment of drugs that affect coagulation and bleeding, since it carries a substantial risk of both thrombosis and hemorrhage. Pharmacologic prophylaxis will always be a tradeoff between preventing venous thrombosis and bleeding risk. The risk of major or critical bleeding with most prophylactic regimens is around 3 percent. Three major groups of drugs are recommended and utilized for thromboprophylaxis:

1. Oral anticoagulants (warfarin/Coumadin)
2. Indirect thrombin inhibitors
   - Unfractionated heparin (UFH)
   - Low molecular weight heparin (LMWH)
   - Pentasaccharides
3. Direct thrombin inhibitors (DTI)
   - Irreversible—hirudin and recombinant hirudins
   - Reversible—melagatran/ximelagatran

The traditional agents for prophylaxis are warfarin, UFH, and LMWH. However, all have limitations that make them less than optimal drugs. The major limitation is inadequate efficacy, and up to 20 percent of THA patients (and up to 50 percent in TKA and HFS) may still develop venous thrombosis. Safety issues, the need for monitoring, and difficulty of administration have given impetus to the search for drugs that are more effective, safer, and easier to administer, particularly in outpatients.

Oral Anticoagulants (Warfarin/Coumadin)

Warfarin is the most frequently used thromboprophylactic agent for major orthopaedic surgery in the United States. It is commenced on the night before surgery or the night of surgery. It has numerous indications in the prevention and treatment of arterial, cardiac, and venous thrombosis. It is a vitamin K antagonist, producing depletion of vitamin KH2, the essential substrate for the γ-carboxylation of the vitamin K-dependent clotting proteins (factors II, VII, IX, and X as well as proteins C and S). The factors produced are deficient and unable to chelate calcium and bind to platelet phospholipids during the clotting process. Warfarin’s onset of action requires the initial clearance of normal clotting factors. Factor VII has a half-life (t1/2) of 6 to 7 h; the onset of anticoagulation may therefore be as early as 24 h. However, a full anticoagulant effect is not achieved until 72 to 96 h because of the longer t1/2 of the other clotting factors. For the same reason, anticoagulation may persist for up to 96 h after stopping warfarin despite a prompt recovery in levels of factor VII. Protein C is rapidly depleted; this may result in an initial thrombogenic phase for the first 48 h of warfarin therapy.

Warfarin has a predictable onset and duration of action but a variable dose-response relationship. It is also subject to numerous drug and dietary interactions.
using the international normalized ratio (INR).\textsuperscript{1,42} The target INR for prophylactic anticoagulation in major orthopaedic surgery is 2 to 3.\textsuperscript{1,2,4,42} This may take some days to achieve from its recommended immediate preoperative or early postoperative commencement.\textsuperscript{5,41,42} This delay in the onset of an anticoagulant effect may explain the marginally inferior performance of warfarin compared with LMWH or adjusted-dose heparin in some trials of VTE prophylaxis in THA.\textsuperscript{1,42} Warfarin appears to be substantially less effective than heparin in TKA but equally effective in HFS.\textsuperscript{3,22,33} These differences reflect different risks for DVT associated with different operations.\textsuperscript{12} Because it is an oral drug, warfarin is ideal for postoperative outpatient use for prolonged prophylaxis, but it requires ongoing INR monitoring and possible dose adjustments. The major complication of warfarin is bleeding, but this appears to be no more common than with other anticoagulants at 1 to 3 percent.\textsuperscript{1,42} Warfarin has been largely abandoned as a prophylactic anticoagulant in Europe because of its delayed onset of action, interpatient variation, inferior efficacy compared to LMWH, drug interactions, and need for frequent monitoring and dose adjustment to maintain the target INR.\textsuperscript{1,42}

**Indirect Thrombin Inhibitors**

Unfractionated heparin (UFH) is a mixture of polysaccharide chains whose molecular weight (MW) varies from 3 to 30 kDa (10 to 50 saccharides in length).\textsuperscript{43} The active pentasaccharide moiety, present on about one-third of the molecules, binds to AT to increase its thrombin inhibitory action some 5000 to 10,000-fold.\textsuperscript{4,43} The larger molecules (>18 saccharides in length) have predominant antithrombin (anti-IIa) activity and are responsible for the platelet binding and interactions of heparin.\textsuperscript{3,43,44} Smaller molecules are unable to bind AT and thrombin simultaneously and have more anti-Xa activity. Unfractionated heparin has an Xa:IIa affinity ratio of around 1 (3 for LMWH).\textsuperscript{5,44} Heparin can then dissociate from AT and be reutilized. At very high doses, UFH may also inhibit IIa via binding with heparin cofactor II.\textsuperscript{43,44} The use of UFH for more than 5 days may lead to nonimmune thrombocytopenia in 1 to 3 percent of patients. This is usually trivial and resolves spontaneously.\textsuperscript{5,6,45-45} A much more feared complication is the immunologically mediated heparin-induced thrombocytopenia (HIT), where antibodies are formed against heparin-platelet factor 4 (PF4) complexes.\textsuperscript{6,43,45} This is seen in 0.1 to 1 percent of patients and results in platelet aggregation and destruction. This, in turn, causes thrombocytopenia and potentially fatal thrombotic events in 10 to 15 percent of patients. Many of these patients will die or require amputation because of arterial or venous thromboses.\textsuperscript{5,47} This condition is then termed heparin-induced thrombocytopenia (HITT). HIT is an emergency, necessitating the withdrawal of all sources of heparin and switching to alternative antithrombotic therapy.\textsuperscript{12,45} A history of HIT contraindicates any future heparin therapy, including LMWHS.\textsuperscript{3,43,45} All patients receiving heparin should have their platelet counts monitored from the fourth or fifth day of therapy. The other complications of heparin therapy include bleeding, heparin resistance, and osteoporosis. Bleeding may be more significant than with equiefficacious doses of other anticoagulants.\textsuperscript{3,45}

Unfractionated heparin has an onset time of 2 h after subcutaneous administration and a 1/2 of 2 h (versus 30 min and 1 h for intravenous administration).\textsuperscript{8,43} The clinical duration of prophylaxis is 4 to 6 h. It is 30 percent bioavailable and may be administered as fixed dose (5000 U/8 to 12 h) or as adjusted doses according to partial thromboplastin time (PTT).\textsuperscript{43} The fixed-dose regimen is more effective than no prophylaxis (27 percent RRR for total DVT in THA) but less effective than other prophylactic anticoagulants.\textsuperscript{8,46} Adjusted-dose UFH (usually by constant intravenous infusion) aims to maintain PTT at or slightly above normal. This technique is highly effective, producing a 74 percent relative risk reduction for overall DVT compared with placebo, but the regular testing is expensive and the technique too labor-intensive for routine use.\textsuperscript{1} For this reason it is no longer recommended by the ACCP.\textsuperscript{1} There is some evidence that a single dose of 1000 U of heparin given intravenously at the time of medullary canal reaming produces a significant reduction in VTE.\textsuperscript{3,14}

**Low-molecular-weight heparins** (LMWHs) are derived from the same animal sources as heparin, by chemical or enzymatic depolymerization.\textsuperscript{41} A range of agents is available with MW of 4 to 6 kDa.\textsuperscript{3,43} Their polysaccharide chains range from 13 to 22 saccharides in length. As such, they have greater anti-Xa than antithrombin activity.\textsuperscript{3,44} This results in little or no impact on PTT.\textsuperscript{3,4} LMWHs have more favorable pharmacokinetic profiles than unfractionated heparin, with 90 to 100 percent bioavailability and half-lives of 2 to 4 h, resulting in a duration of clinical effect of around 12 h.\textsuperscript{8,44} They achieve peak anticoagulation 3 to 4 h after subcutaneous administration and are cleared renally. Doses should be adjusted where renal function is impaired.\textsuperscript{8,44} The risk-benefit ratio (bleeding versus thromboprophylaxis) is superior to that of UFH and the low-molecular-weight forms produce significantly less HIT and osteoporosis than the UFHs and less bleeding complications at equiefficacious doses.\textsuperscript{3}

LMWHs perform as well as or better than warfarin or UFH across the range of major orthopaedic procedures.\textsuperscript{3,7,12,16,25,32,37,38} The advantage is likely due to a more rapid onset of anticoagulant effect. They reduce the risk of DVT by 70 percent in THA, 52 percent in TKA, and 44 percent in HFS.\textsuperscript{3,1,14} These figures are obtained
with once- or twice-daily regimens (e.g., 40 mg enoxaparin daily starting 12 h preoperatively or 30 mg twice daily starting 12 to 24 h postoperatively). Preoperative initiation of LMWH therapy is no more effective than early postoperative commencement.\textsuperscript{3,25} There is little increase in the antithrombotic benefit of the 60-mg daily dose but an increased bleeding risk.\textsuperscript{5,8} It would therefore appear that a 40-mg daily dose is optimal in terms of risk-benefit ratio. There is good evidence that a further improvement in antithrombotic effect can be achieved without an increase in bleeding risk if the initial dose of LMWH is administered within 6 to 8 h of skin closure at half of the normal high-risk dose followed by a full dose daily thereafter.\textsuperscript{12,25,39,47} Earlier postoperative or immediate preoperative administration is associated with an unacceptable bleeding risk.\textsuperscript{39,47} Current recommendations for prophylaxis are a fixed daily dose of LMWH for 7 to 10 days after major orthopaedic surgery (up to 4 weeks after hip surgery).\textsuperscript{1,19,21} Monitoring is not required.\textsuperscript{1,16} Should it become necessary, PTT will usually be unaffected and anti-Xa activity may be measured. It is prudent to decrease LMWH doses in elderly patients with impaired renal function and in those weighing less than 50 kg.\textsuperscript{8,48,49}

Pentasaccharides, of which the prototype is fondaparinux, are synthetic molecules with pure anti-Xa effect mediated entirely via reversible binding to AT.\textsuperscript{1,15,50} Fondaparinux increases AT activity 300-fold.\textsuperscript{50} The fondaparinux-AT complex binds irreversibly with Xa and inhibits its action. Fondaparinux then dissociates from the complex and is free to activate another AT molecule.\textsuperscript{50} This represents a catalytic reaction compared to the stoichiometric mechanism of action of direct thrombin inhibitors (DTI), in which each molecule can inhibit only a single thrombin molecule.\textsuperscript{50} Factor Xa is the pivotal step in the coagulation pathway, the junction of intrinsic and extrinsic pathways. One molecule of Xa activates 50 molecules of thrombin.\textsuperscript{50} Factor Xa inhibition results in linear, dose-dependent, and predictable inhibition of thrombin formation.\textsuperscript{51} Fondaparinux can inhibit both free and clot bound Xa; it therefore prevents de novo clot formation and growth of existing thrombi.\textsuperscript{50,51} It does, however, permit the formation of a certain amount of normal thrombin, which may allow effective primary hemostasis, normal wound healing (where thrombin is thought to have a role), and activation of endogenous protein C via thrombin—thrombomodulin binding.\textsuperscript{50} Hence, endogenous anticoagulant activity is preserved.\textsuperscript{15,50} In addition, fondaparinux does not bind to platelets, cause thrombocytopenia, or cross-react with sera of HIT patients.\textsuperscript{15,52} It does not inhibit osteoblasts or cause elevation of liver enzymes.\textsuperscript{50,52} The risk of major bleeding at a fixed daily dose of 2.5 mg is not different from that associated with UFH or LMWH, but its long half-life and lack of reversibility imply that bleeding with fondaparinux may be more difficult to manage than with heparin.\textsuperscript{5,51}

Fondaparinux is fully absorbed from a subcutaneous injection. Onset of action is 1 to 3 h after administration, and the \(t_{1/2}\) is about 17 h. The kidneys excrete it almost entirely. There is minimal intra- and intersubject variability; therefore routine monitoring and dose adjustments are not necessary unless creatinine clearance is less than 30 mL/min.\textsuperscript{8,15,17} It is not registered for use in patients under 50 kg. The drug is given as a single daily dose of 2.5 mg, starting 6 to 8 h after the operation for best balance of antithrombotic effect and bleeding risk.\textsuperscript{15,17} It is currently registered for up to 9 days of postoperative use, but there is overwhelming evidence of further benefit if therapy is prolonged up to 4 weeks postoperatively. A 4-week prophylactic regimen produces a 96 percent reduction in VTE compared with 1 week of fondaparinux followed by 3 weeks of placebo.\textsuperscript{13,17,23,53} The overall risk reduction for fondaparinux versus conventional enoxaparin regimens is 55.2 percent, with no clinically important increase in bleeding.\textsuperscript{15,17,23} Idraparinux is a derivative of fondaparinux that is currently under investigation for long-term prophylaxis.\textsuperscript{9,17} It has a \(t_{1/2}\) of 130 h and is administered as a 2.5-mg subcutaneous injection once weekly. At this dose, it appears to cause less bleeding complications than warfarin, adjusted to an INR of 2 to 3. Bleeding management poses the same problems that apply to fondaparinux.\textsuperscript{9,17}

**Direct Thrombin Inhibitors**

These drugs bind irreversibly (hirudin and recombinant hirudins; e.g., desirudin) or reversibly (melagatran/ximelagatran, dabigatran etexilate) to the active catalytic site of thrombin.\textsuperscript{6,15} All the physiologic functions of thrombin are inhibited, including conversion of fibrinogen to fibrin, fibrin cross-linking, feedback activation of clotting cascades, protein C and platelet activation, and inhibition of fibrinolysis.\textsuperscript{2,6} Direct thrombin inhibitors can inhibit both free and clot-bound thrombin, especially the smaller molecules like melagatran, which inhibit them in a ratio of 1:1.\textsuperscript{2,6,15} They therefore prevent growth of existing clots and inhibit de novo thrombus formation.\textsuperscript{6,35} The reversible agents allow periods of normal thrombin activity to facilitate normal hemostasis.\textsuperscript{6} The action of DTIs is a direct stoichiometric inhibition of thrombin, which does not require AT; they are therefore effective in AT deficiency.\textsuperscript{6,15} The antithrombotic efficacy of DTI is at least as good as that of LMWH or warfarin, and some trials point to a 20 to 30 percent advantage over warfarin. They do not produce HIT and are therefore indicated for anticoagulation in patients with a history of HIT.\textsuperscript{2,6} At doses producing equivalent antithrombotic effect, bleeding is less than with UFH or warfarin.\textsuperscript{6} The drugs are predominantly excreted by the kidneys and dose adjustment is required in severe renal impairment.\textsuperscript{2} Transient elevation
of liver transaminases is seen in 6 to 13 percent of patients; a twofold elevation in this variable is an indication to discontinue DTI and use another anticoagulant.6,26

The two DTIs that have undergone extensive testing for prophylaxis against thrombosis in major orthopaedic surgery are desirudin and melagatran/ximelagatan.6,54 Desirudin is given as a twice-daily fixed dose of 15 mg subcutaneously. It has a t1/2 of 4 to 8 h. Monitoring of its anticoagulant effect is not indicated. When started 30 min before surgery, it resulted in a threefold reduction in thrombosis versus UFH and a 25 percent advantage over 40 mg of enoxaparin daily.6,54 Part of this advantage may be due to the more efficient anticoagulant effect of the DTI, but the administration very soon before surgery probably also plays a role.6,54 Owing to its high cost, desirudin is usually reserved for prophylaxis in HIT patients. Melagatran is a small, reversible parenteral DTI, which is also available as an oral prodrug, ximelagatan.2,54 It has a t1/2 of 4 to 5 h and is administered twice daily. It acts rapidly after oral or subcutaneous administration.2,6,54 This, and the short t1/2, means that anticoagulation can be reversed rapidly in cases of excessive bleeding, but it can be reestablished quickly.2,6 Diuresis promotes clearance and offset of action.6 Various regimens are used for thrombosis prophylaxis and all are comparable or superior to warfarin.6,26 High-dose regimens, especially where prophylaxis is started soon before surgery, have achieved a 25 percent reduction in VTE compared with LMWH, but at the cost of increased noncritical bleeding.2,6 In Europe, treatment with subcutaneous melagatran (2 mg) is started 4 to 8 h postoperatively, followed by 3 mg 12 h later and then 24 mg of ximelagatan orally twice daily.2,6 In the United States, oral ximelagatan 24 to 36 mg is administered twice daily, starting 12 to 24 h postoperatively.2,6 The 24-mg dose reduces VTE rates to a similar extent as adjusted doses of warfarin (but less so than LMWH), and the 36-mg dose shows a 20 to 30 percent improvement over warfarin.2 Ximelagatan has a substantially wider therapeutic range than warfarin. No monitoring of anticoagulant effect is required.2,15

**Recommendations for Thromboprophylaxis in Major Orthopaedic Surgery**

Routine prophylaxis has been standard in major orthopaedic surgery for more than 15 years.8 This is not surprising, since without prophylaxis VTE rates are unacceptably high. Even with current prophylaxis, 1.5 to 10 percent of patients suffer symptomatic venous thrombosis within 3 months of surgery. Some occur after silent DVT already present in the hospital, but many occur primarily after discharge. It is thus impossible to predict, with routine screening on discharge, which patients will develop VTE.8,16,17 The following recommendations for prophylaxis are those of the seventh ACCP consensus conference.1 They are based on an exhaustive analysis of almost 800 published trials for which the strength of evidence for benefit or risk, and the methodologic quality of the studies was taken into account. Where there is certainty of benefit or risk, the evidence is classified as grade 1 and a “recommendation” is made. Where evidence is less certain, it is termed grade 2 and a therapeutic “suggestion” is made. Randomized controlled trials with consistent results are classified as grade A, while those with less consistent results or methodologic flaws are designated grade B. Data from observational studies or extrapolated from a group in a randomized trial to another similar group of patients are labeled grade C.

Where the grade C observations or data are particularly compelling or secure, they are classified as grade C+. Grade C+ recommendations are regarded as stronger than grade B. Overall, therefore, recommendations may fall anywhere from grade 1A to grade 2C, with progressively declining validity and strength.55

For THA, the following list of prophylactic antithrombics constitutes a grade 1A recommendation (see Chap. 10).1 Any one of the following three regimens can be used:

1. **LMWH at the usual high-risk dose** (e.g., enoxaparin 30 mg twice daily or 40 mg daily). Administration is started 12 h preoperatively or 12 to 24 h postoperatively. Alternatively, a half dose (e.g., dalteparin 2500 IU) may be administered 4 to 6 h postoperatively and the full dose continued daily thereafter.1,39,47
2. **Fondaparinux 2.5 mg subcutaneously daily**, commencing 6 to 8 h postoperatively.1,5
3. **Warfarin, starting preoperatively or the evening after surgery to a target INR of 2 to 3.1**

The recommendations carry equal weight, since the prophylactic advantages of fondaparinux and LMWH are balanced by a slightly higher bleeding risk. Grade 1A recommendations are made against the use of aspirin, dextran, low-dose unfractionated heparin, graded elastic stockings, IPC, and plantar plexus compression as sole prophylactic options.1

In TKA, the incidence of symptomatic and proximal DVT is lower despite the higher overall incidence of venous thrombosis seen by venography (see Chap. 11).5 Prophylaxis is less effective than in THA,12 although a substantial benefit exists for fondaparinux over LMWH and for LMWH over warfarin.1 This must be balanced by the potential severity of the consequences of local bleeding. The same grade 1A recommendations made for hip arthroplasty apply to TKA.1 However, optimal use of IPC as a sole option receives a grade 1B recommendation.
where anticoagulants cannot be used. Aspirin and UFH are not recommended (grade 1A). The same applies to planar plexus compression (grade 1B). Knee arthroscopy requires no drug prophylaxis. Early mobilization is sufficient unless the patient has other risk factors, in which case LMWH is recommended.1

Hip fracture surgery has the highest risk of major symptomatic venous thrombosis and PE (see Chap 16).1 Routine prophylaxis is mandatory in all cases. Unlike THA and TKA, the thrombogenic event has already occurred preoperatively, and preoperative prophylaxis is recommended unless immediate surgery is planned (grade 1C).56 The prophylactic recommendations are fondaparinux (grade 1A), LMWH (grade 1C), warfarin (grade 2A), and low-dose UFH (grade 1B).1 Where anticoagulants are contraindicated, properly applied mechanical prophylaxis is a grade 1C recommendation.1,13

The ACCP have also formulated recommendations for other orthopaedic procedures.1 They recommend against prophylaxis in elective spinal surgery (grade 1C) unless additional risk factors exist (e.g., malignancy or previous thrombosis) (see Chap. 14). Should these be present, they make a grade 1B recommendation for the use of UFH, LMWH, or IPC alone.1 With acute spinal cord injury, however, routine prophylaxis is a grade 1A recommendation because of the excessive thrombotic risk posed by this lesion. Until primary hemostasis has been achieved, this should be with mechanical methods. Thereafter, LMWH is the method of choice.1,12 Extended prophylaxis is advised during rehabilitation (grade 1C). This can be achieved with either long-term LMWH or warfarin.1

In isolated lower limb fractures other than the hip, no prophylaxis is recommended (grade 2A) (see Chap. 16).1 In trauma, routine prophylaxis is a grade 1A recommendation if the patient has one or more VTE risk factors (see Chaps. 2 and 16).1,12 LMWH is the agent of choice once adequate hemostasis is established. In the interim, mechanical methods can be employed (grade 1B). Prophylaxis should be continued until discharge (grade 1C).1

Recommendations have also been made for the initiation, timing, and duration of prophylaxis and the use of predischarge screening.1 There appears to be little advantage to starting prophylaxis preoperatively, although the regimen remains an acceptable one. The best prophylaxis is achieved when it is started between 2 h preoperatively and 6 to 8 h after the operation. The latter time may offer the best tradeoff between efficacy and bleeding risk. If LMWH is used, the dose administered at this time is half of the normal high-risk dose. With fondaparinux, current recommendations are that the full 2.5-mg prophylactic dose be administered. Patients at particularly high risk for bleeding should receive the first dose of anticoagulants between 12 and 24 h after surgery. In this case, reduced prophylactic efficacy is balanced by a reduced risk of bleeding.1

There is consensus in the ACCP that there is no clinical or cost benefit in routine screening, particularly Doppler examinations, at or after discharge to determine in which patients prophylaxis should be continued.1,12 It is known that a substantial proportion of patients leave the hospital with a clinically silent DVT and that the risk of new thrombus formation persists for 4 to 12 weeks after hip surgery (shorter with TKA).5,11,12 About 45 to 80 percent of thromboses associated with hip and knee arthroplasty occur after discharge. The major factors that predict rehospitalization with thrombosis are a previous history of venous thrombosis, obesity, and advanced age.1,12 Extended thromboprophylaxis (28 to 35 days), especially in hip surgery, results in a risk reduction for symptomatic thrombosis of about 60 percent.5,30 Economic studies have indicated that extended prophylaxis after discharge may be cost-effective compared with only in-hospital prophylaxis.33 The current grade 1A recommendations for all major orthopaedic procedures are for 10 days of prophylaxis with current agents.1 With THR and HFS, this should be continued until 28 to 35 days postoperatively.5,10,21 The agents of choice for THR are LMWH or warfarin (recommendation for both grade 1A) or fondaparinux (grade 1C+). For hip fracture surgery, fondaparinux is a grade 1A recommendation; LMWH and warfarin are grade 1C+.1,17 At the time of the ACCP consensus conference, ximelagatran was not yet registered for prophylaxis, therefore no recommendations were made for its use.1,17

**IMPACT OF ANESTHESIA ON VENOUS THROMBOEMBOLISM**

Neuraxial anesthesia (spinal or epidural) has been associated with consistent and substantial reductions in DVT incidence in major orthopaedic surgery (see Chap. 30).5 This is most evident when other prophylactic measures are not used.57 Reductions of 50 percent in proximal DVT have been confirmed venographically in patients who underwent TKA or THA under epidural anesthesia (see Chaps. 10 and 11).5,58 The impact on overall DVT in TKA patients is less significant, possibly because the use of a tourniquet counteracts the beneficial effect of neuraxial anesthesia on venous blood flow.58 Neuraxial anesthesia is the only intervention that is associated with reduced DVT and reduced perioperative bleeding and transfusion requirements.57

Various mechanisms are postulated to explain the impact of neuraxial anesthesia on thrombosis. These include a beneficial effect on arterial and venous blood flow in the lower limbs due to sympathetic block, an endothelial protective effect, and direct inhibition of coagulation or platelet function by absorbed local anesthetic.53,57 However, a significant direct anticoagulant or
antiplatelet effect is unlikely, because the plasma concentrations of local anesthetic, even during constant epidural infusions, are lower than those required to produce in vitro anticoagulation. In addition, the reduced bleeding associated with neuraxial anesthesia is incompatible with a clinically important anticoagulant effect. Implications of prophylaxis on choice of anesthesia

The hemorrhagic complications of anticoagulant prophylaxis are not restricted to the surgical site. Bleeding may be caused by other invasive procedures. As mentioned, a significant proportion of major orthopaedic operations are performed under neuraxial anesthesia. This may be continued postoperatively by local anesthetic infusions through a catheter. Many other patients receive plexus or peripheral nerve blocks with or without indwelling catheters.

Vertebral canal hematoma (VCH) is defined as symptomatic bleeding within the spinal neuraxis. It is a rare but catastrophic complication of neuraxial anesthesia, anticoagulation, and the combination thereof. These hematomas present an average of 3 days after anticoagulant therapy is started. Almost 70 percent of cases present with a new progressive sensory or motor deficit. Only 38 percent of patients have a good or fair outcome after VCH. This figure increases to 75 percent when surgical decompression is done within 8 h of the onset of symptoms. Hematomas of the vertebral column account for 50 percent of spinal injuries associated with anesthesia. Spinal injuries were the leading cause of legal claims against anesthesiologists in the United States in the 1990s. Anesthetic care in cases of VCH was judged adequate in only 7.5 percent of cases, and settlements were generally high.

The incidence of VCH is difficult to determine because of regional differences in thromboprophylactic drug use and protocols, varying levels of compliance with guidelines, and the likelihood of underreporting. VCH was rare worldwide, with an incidence not exceeding 1:150,000 for epidural and 1:220,000 for spinal anesthesia, until the release of LMWH in North America in the early 1990s. Since that time, over 80 cases have been reported to the Medwatch system, most of them in the first 5 years of this period. The estimated incidence of VCH at this time was about 1:3000 in epidural anesthesia and 1:40,000 in spinal anesthesia. Since 1998, there appears to have been a slowing of reports. This may represent increased compliance with guidelines for the concomitant use of neuraxial anesthesia and anticoagulants. The most recent of these guidelines were formulated by the Second American Society of Regional Anesthesia (ASRA) Consensus Conference on Neuraxial Anesthesia and Anticoagulation of 2002.

There are several risk factors identified for the development of VCH:

1. Elderly women undergoing major orthopaedic surgery under neuraxial anesthesia account for 75 percent of cases of VCH.
2. Hemostatic abnormalities were present in 68 percent of cases. These included administration of excessive doses of anticoagulants, administration close to the time of neuraxial procedures, combinations of anticoagulant drugs, and use of these drugs in patients with hepatic or renal impairment.
3. Difficulties with needle placement: traumatic insertion or bleeding on insertion were encountered in half of the patients. A combination of this factor plus a hemostatic abnormality was seen in 87 percent of cases.
4. Epidural anesthesia accounts for about 75 percent of cases and spinal anesthesia for 25 percent. In Europe, spinal anesthesia is used about four times as often as epidural anesthesia, but epidural anesthesia still accounts for the majority of VCH cases.
5. Two-thirds of cases were associated with neuraxial catheter techniques.
6. Fully 47 percent of VCH cases followed catheter removal. This is therefore no less risky than the initial neuraxial puncture.
7. Many patients received other drugs with an effect on clotting in addition to their prophylactic anticoagulants. Nonsteroidal anti-inflammatory agents and antipatelet agents were most commonly implicated.
8. The choice and dose of anticoagulant and timing with respect to the neuraxial puncture or catheter removal are of critical importance.\(^{40}\)

There have been five case reports of VCH associated with UFH and four in patients who received warfarin.\(^{8,41,59}\) All of the latter occurred when the epidural catheter was removed. However, the vast majority of cases of VCH (more than 80) have been reported to be associated with LMWH prophylaxis.\(^{40}\) There appears to be no advantage of one LMWH preparation over any other in terms of risk for VCH.\(^{40}\) The majority of VCH cases have occurred when LMWH was given twice a day.\(^{3}\) This means that many of patients had unsafe levels of anticoagulation when catheters were removed, since no true nadir in anticoagulant level could occur.\(^{40,60}\) These patients receive 50 percent more LMWH than patients on a once-daily regimen. There appears to be no major advantage in starting prophylaxis preoperatively. Neuraxial puncture can therefore be performed entirely in the absence of anticoagulation.\(^{40}\)

There is much controversy about the impact of antiplatelet agents on VCH. It appears that aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in themselves do not pose a risk for VCH.\(^{40,59}\) When they are combined with other anticoagulants, however, the risk of VCH increases by an unspecified amount.\(^{40,59}\) Such combinations are not prohibited, but they make it mandatory to follow dosing guidelines closely. Other antiplatelet agents—such as thienopyridines (clopidogrel, ticlopidine) and platelet glycoprotein IIb/IIIa inhibitors (abciximab, epifibatide, tirofiban)—have more profound and multimodal antiplatelet activity. They must be discontinued 5 to 14 days before surgery and, although specific guidelines are lacking, are probably incompatible with other anticoagulants for safe surgery or neuraxial anesthesia.\(^{40}\)

No case reports or recommendations exist at present for the DTI melagatran/ximelagatran, although it has been used in conjunction with neuraxial anesthesia in major orthopaedic surgery in over 2000 patients.\(^{2,40}\) Fondaparinux has not been associated with VCH in more than 3600 neuraxial blocks for major orthopaedic surgery.\(^{17,40,52,61}\) In these trials, single-injection neuraxial anesthetics were employed; scrupulous attention was paid to exclude patients with traumatic blocks and to dosing initiation and intervals. At this stage, it is impossible to confirm the safety of catheter techniques with this drug.\(^{40}\)

The ASRA consensus conference of 2002 has produced guidelines to maximize safety when neuraxial anesthesia/analgesia is used concomitantly with anticoagulants.\(^{40}\)

1. Unfractionated heparin at low doses is compatible with neuraxial anesthesia and catheter techniques. It should, however, be delayed for at least an hour after the neuraxial procedure. Catheter removal should occur 2 h or more after a preceding dose and at least 1 h before one. A bloody tap may indicate that surgery should be postponed, but decisions should be made on an individual basis. Platelet counts should be checked on day 5 of UFH therapy.\(^{8,40}\)

2. There is virtually no evidence that a once-daily LMWH regimen started at least 6 to 8 h or more after the operation places the patient at increased risk for VCH.\(^{8,59}\) Indwelling catheters are safe provided that they are removed no sooner than 10 to 12 h after the previous dose of LMWH and at least 2 h before the next dose.\(^{59}\) Should preoperative LMWH be used, it must be given at least 10 to 12 h before the neuraxial procedure.\(^{59}\) If twice-daily LMWH administration is planned, it should be started no sooner than 24 h after surgery and at least 2 h after removal of the epidural catheter.\(^{59}\) Twice-daily regimens are not safe with indwelling neuraxial catheters.\(^{5,59}\) Traumatic insertion or a bloody spinal tap does not make it necessary to postpone surgery but requires delay of the first dose of LMWH for 24 h.\(^{59}\)

3. Warfarin has been associated with VCH only when started preoperatively.\(^{41}\) All cases occurred on removal of the epidural catheter and all had INR values of >1.5.\(^{59}\) It is advisable to check the INR before performing a neuraxial block if warfarin has been started more than 24 h preoperatively because of the unpredictability of its dose-response relationship. Likewise, INR should be measured while an indwelling neuraxial catheter is in place or before its removal.\(^{59}\) An INR of >3 requires withholding of warfarin until it has fallen to 1.5. The latter value corresponds with a factor VII level of 40 percent of baseline.\(^{40}\) At this level, the catheter can be removed safely.\(^{59}\) Since the target INR level for prophylaxis is 2 to 3, warfarin prophylaxis is not readily compatible with the use of indwelling neuraxial catheters.\(^{40,41}\)

Because VCH is so rare, it is not possible to perform a prospective study of sufficient power to guide practice.\(^{40,59}\) We therefore, must rely on a consensus derived from the collective experience of experts in the field. This consensus cautions the practitioner to weigh decisions to combine neuraxial techniques and anticoagulation on an individual basis.\(^{8}\) Every attempt should be made to ensure that all neuraxial interventions are carried out when the coagulation status is normal or nearly normal.\(^{59}\) This is best achieved by adherence to guidelines, giving particular attention to factors that may enhance anticoagulant effect. These are advanced age; low body mass; hepatic, renal, or cardiac disease; drug
interactions, and concomitant use of other drugs with a potential for anticoagulant effects. Should the safety of neuraxial anesthesia be uncertain in a particular patient, it is prudent to err on the side of caution and to avoid neuraxial blockade. Should a neuraxial block be indicated by the patient’s medical condition and the coagulation status be questionable, a single injection spinal block with a small-gauge needle is the technique of choice. In all patients in whom anticoagulation is used concomitantly with any neuraxial technique, monitoring is mandatory until at least 24 h after the termination of the block or catheter removal. Any symptoms or signs of cord compression dictate emergency radiologic investigation to confirm or exclude VCH, followed by immediate compulsory decompression in all cases. Using the lowest effective concentration of local anesthetic so as to avoid motor block facilitates monitoring during continuous infusion of local anesthetic via an indwelling catheter. Motor function can then be monitored on an ongoing basis.

The precise risk associated with plexus and peripheral nerve blocks in the presence of anticoagulants is unclear. The frequency and severity of hemorrhagic complications is unknown. Case reports have confirmed the possibility of major, critical, and even fatal bleeding in this situation. The bleeds have been associated with UFH, LMWH, and thienopyridine drugs. All such reports relate to psoas compartment or lumbar sympathetic block. Significant bleeds requiring transfusion are possible, since the psoas compartment can accommodate up to 3 L of blood. Neurologic deficits are usually minimal and reversible within a maximum of 6 to 12 months. Since most nerve sheaths do not lie in non-expandable compartments, the likelihood of irreversible neural ischemia is far smaller than in the spinal cord. At this stage, consensus statements regarding neuraxial anesthesia are applied to deep plexus blocks. It is unclear at present whether this policy is too restrictive.

REFERENCES


