Coagulation and Thromboembolism

Venous thromboembolic disease and prophylaxis are subjects of controversy in orthopaedic surgery. Venous thromboembolism is a major risk in patients undergoing total hip and knee arthroplasty as well as repair of a hip fracture. In addition, patients sustaining major orthopaedic trauma including spinal cord injury as well as patients undergoing treatment of various other musculoskeletal conditions are at potential risk for thromboembolism. Morbidity and mortality are associated with both thromboembolic disease and prophylaxis.

Various forms of pharmacologic and mechanical prophylaxis are available and are presented in the American Academy of Orthopaedic Surgeons’ guideline on prevention of pulmonary embolism.1 This clinical practice guideline was based on a systematic review of published studies of patients undergoing total hip and total knee arthroplasty to prevent pulmonary embolism.2 The guideline found no difference in the pulmonary embolism rate, death rate, or death related to bleeding from prophylaxis among different thromboembolic prophylactic measures1 (Table 1).

The Surgical Care Improvement Program (SCIP) of the Centers for Medicare and Medicaid Services (CMS) was initiated in an attempt to minimize venous thromboembolic disease and includes pay-for performance programs. This program has focused additional attention on thromboembolic treatment. Specifics of the basic guidelines will be presented later in this chapter. A 2008 study determined the incidence, risk factors, and long-term sequelae of postoperative hematomas requiring surgical evacuation after primary total knee arthroplasty and pointed out the potential for adverse sequela of anticoagulation.3 The authors found a significantly increased risk of the development of deep infection and/or subsequent major surgery in patients who returned to the operating room within 30 days after the index total knee arthroplasty for evacuation of a postoperative hematoma. The authors concluded that these results support all efforts to minimize the risk of postoperative hematoma formation. Consequently, when patients are managed with pharmacologic prophylaxis it is important to prevent the development of a postoperative hematoma, to monitor for the development of a hematoma, and to practice techniques that will minimize its occurrence.

One study found that patients treated with aspirin or warfarin were somewhat less likely to have associated bleeding complications than were patients treated with low-molecular-weight heparin (LMWH) or subcutaneous heparin.4

Pharmacologic Prophylaxis

The ideal prophylactic agent should be effective, have minimal adverse effects, not require monitoring, be administered orally, and be cost-effective.5 Of all of the interventions (reviewed by the Agency for Healthcare Research and Quality [AHRQ]) in terms of the ability to reduce adverse events while decreasing overall costs, prophylaxis for deep venous thrombosis has received the highest safety rating.5

The four most common pharmacologic prophylaxis agents used in the United States are warfarin, LMWH, pentasaccharide, and aspirin (acetylsalicylic acid). It is important to appreciate the evidence supporting the use of the various pharmacologic prophylactic agents. Evidence-based medicine typically includes a level of evidence as well as an indication of the strength of a recommendation. Table 2 describes the levels of evidence commonly cited in the medical literature, including The Journal of Bone and Joint Surgery. The levels range from level I, which includes a high-quality randomized trial, to level V, expert opinion. Strengths of recommendation (Table 3) range from grade A, which
Table 1

American Academy of Orthopaedic Surgeons Clinical Practice Guideline on the Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty: Summary of Recommendations

Recommendation 3.3
Chemoprophylaxis of patients undergoing hip or knee replacement

Recommendation 3.3.1
Patients at standard risk for both PE and major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including, in alphabetical order: aspirin, LMWH, synthetic pentasaccharides, and warfarin. (Level III, Grade B [choice of prophylactic agent], Grade C [dosage and timing])

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature defining a clearly superior regimen.

Recommendation 3.3.2
Patients at elevated (above standard) risk for PE and at standard risk for major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including, in alphabetical order: LMWH, synthetic pentasaccharides, and warfarin. (Level III, Grade B [choice of prophylactic agent], Grade C [dosage and timing])

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations.

Recommendation 3.3.3
Patients at standard risk for PE and at elevated (above standard) risk for major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including, in alphabetical order: aspirin, warfarin, or none. (Level III, Grade C)

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations.

Recommendation 3.3.4
Patients at elevated (above standard) risk for both PE and major bleeding should be considered for one of the chemoprophylactic agents evaluated in this guideline, including, in alphabetical order: aspirin, warfarin, or none. (Level III, Grade C)

Note: The grade of recommendation was reduced from B to C for dosage and timing because of the lack of consistent evidence in the literature on risk stratification of patient populations. No studies currently include patients at elevated risk for major bleeding and/or pulmonary embolism (PE) in study groups.


Table 2

Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High-quality randomized trial</td>
</tr>
<tr>
<td>II</td>
<td>Cohort study (good control)</td>
</tr>
<tr>
<td>III</td>
<td>Case-control study</td>
</tr>
<tr>
<td>IV</td>
<td>Uncontrolled case series</td>
</tr>
<tr>
<td>V</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>


Table 3

Strengths of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Good evidence: level I studies with consistent findings (adequate quality and applicability)</td>
</tr>
<tr>
<td>B</td>
<td>Fair evidence: level II or III studies with consistent findings (adequate quality and applicability)</td>
</tr>
<tr>
<td>C</td>
<td>Poor evidence: level IV or V studies with consistent findings</td>
</tr>
<tr>
<td>D</td>
<td>Insufficient or conflicting evidence not allowing a recommendation</td>
</tr>
</tbody>
</table>


consists of good evidence based on level I studies with consistent findings that have adequate quality, to grade D, in which there is insufficient or conflicting evidence that precludes a recommendation.

Warfarin

Warfarin is a vitamin K antagonist that is attractive because it is an oral agent. Based on the American College of Chest Physicians (ACCP) Guidelines6 there is grade IA data supporting its use in prophylaxis in patients undergoing elective hip replacement and elective knee replacement, with an international normalized ratio (INR) target of 2.5 and a range from 2.0 to 3.0. It is also effective in the prophylaxis of patients undergoing hip fracture surgery with a grade of IB when the INR range is 2.0 to 3.0 with a target of 2.5. Limitations of warfarin include the need for monitoring, interaction with other drugs, and variable metabolism based on a genetic basis; it has a long half-life and its effects are difficult to reverse.
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Low-Molecular-Weight Heparin
LMWH is attractive because it has rapid antithrombotic activity and a half-life of approximately 4.5 hours. LMWH does not require regular monitoring; however, it is associated with increased cost and a risk of bleeding. All heparin agents have some risk of heparin-induced thrombocytopenia as well as a higher risk of postoperative drainage. According to one study, there was a significantly increased risk of “minor” bleeding events in patients undergoing total hip replacement in comparison with patients who received warfarin prophylaxis. According to the ACCP guidelines there is grade IA data for prophylaxis with LMWH for patients undergoing elective hip replacement, elective knee replacement, and hip fracture surgery. However, one study showed both low efficacy and a high complication rate with the enoxaparin protocol.

Mechanical Prophylaxis
Mechanical prophylaxis primarily consists of compressive devices that provide prophylaxis by decreasing venous stasis and increasing fibrinolysis. One of the major drawbacks of compression devices is compliance, not only in terms of the amount of time in which the patient is in the device, but also how effectively the device is applied to the extremity. A 2006 study of 275 patients undergoing unilateral total knee replacement evaluated the use of a mechanical compression device and aspirin compared with enoxaparin for prophylaxis following total knee replacement and found that when used in combination with pneumatic compression, enoxaparin was not superior to aspirin in preventing deep venous thrombosis.

Inferior Vena Cava Filter
An inferior vena cava (IVC) filter functions by preventing a pulmonary embolus as opposed to preventing a deep venous thrombosis. Typically, this device is indicated for patients with a previous history of deep venous thrombosis and/or pulmonary embolism as well as those who sustain major trauma and in whom pharmacologic prophylaxis is contraindicated. IVC devices are expensive. Retrievable devices are now available.

Aspirin
Aspirin is a safe, inexpensive oral agent that does not require monitoring. However, it is less effective in terms of prophylaxis when used alone. A prospective randomized study was conducted comparing treatment with LMWH and a calf mechanical compression device along with aspirin. The rates of deep venous thrombosis were assessed with ultrasonography and there were no significant differences between the two groups, showing that aspirin in combination with mechanical compression may be as effective as and safer than more aggressive anticoagulant therapy.

Thromboembolic Disease After Spine Surgery
An evidence-based analysis of thromboprophylaxis in patients with acute spinal injuries was performed. The authors studied patients who underwent surgery following spinal injury and compared the groups with and without spinal cord injury. The authors found an increased incidence of deep venous thrombosis in patients with spinal cord injury compared to those without. They recommended that prophylaxis begin as soon as possible once it is deemed safe in terms of bleeding potential. Further, the authors found that the use of LMWH was more effective with respect to deep venous thrombosis prophylaxis than unfractionated heparin with less bleeding. In addition, it was concluded that prevention of pulmonary embolism appeared successful with the use of vitamin K antagonists.

The American Academy of Orthopaedic Surgeons Clinical Guideline on Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty1 recommendations are based on an assessment of the patient risk for pulmonary embolism and the risk for major bleeding. The guideline stratified patients into one of four categories based on whether the patient has a standard or elevated risk of pulmonary embolism and a standard or elevated risk of major bleeding, hence the recommendations are patient specific (Table 4). Patients at standard risk for both pulmonary embolism and major bleeding should be considered for treatment with one of the following chemoprophylactic agents, listed in alphabetical order: aspirin, LMWH, synthetic pentasaccharide, and warfarin. Patients at an elevated risk for pulmonary embo-
risk for both pulmonary embolism and major bleeding should be considered for prophylaxis with aspirin, warfarin, or neither agent. In addition, patients should be considered for intraoperative and postoperative mechanical compression. Patients with known contraindications to anticoagulation should be considered for vena cava filter placement.

The AAOS clinical guideline provides additional recommendations based on the results of the objective AAOS Consensus Process in which the work group members participated, and these recommendations are provided in Table 5. General recommendations include use of an IVC filter in patients who have contraindications to anticoagulation, rapid patient mobilization, and educating patients about symptoms of thromboembolism after discharge.

A risk assessment was performed for patients undergoing total hip and knee arthroplasties, and a multimodal protocol for thromboprophylaxis was developed. Patients were divided into two groups based on low or high risk. Low risk factors are cardiac disease (congestive heart failure) classified as class I (according to the system of the New York Heart Association), prior deep venous thrombosis that occurred more than 5 years previously, inactive malignant disease, current use of hormone replacement therapy (HRT), chronic tobacco use, and blood disorders consisting of sickle cell trait, polycythemia vera, or thrombocytopenia. Some patients had a combination of these risk factors. High risk factors are a history of a venous thromboembolic event that occurred within the previous 5 years, congestive heart failure classified as class II or III according to the system of the New York Heart Association, atrial fibrillation with cardiac disease and the use of warfarin, recent surgery for the treatment of malignant disease, or current adjuvant drug therapy and thrombophilia, including factor V Leiden, prothrombin disorders, protein-S deficiency, antithrombin disorders, or hypercoagulability states. In addition, some patients had a combination of these factors. Low-risk patients were managed with aspirin, dipyridamole, or clopidogrel bisulfate as well as intermittent pneumatic calf compression devices. High-risk patients were managed with LMWH or warfarin and intermittent calf compression. The authors concluded that a multimodal thromboembolic prophylactic regimen is consistent with protecting patients while limiting adverse clinical outcomes secondary to thromboembolic, vascular, and bleeding complications. The level of evidence was therapeutic level III.

### Table 4

<table>
<thead>
<tr>
<th>General Recommendations Derived With the Consensus Process</th>
<th>Level of Evidence/Strength of Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Assess all patients preoperatively to determine whether risk of pulmonary embolism is standard or high</td>
<td>III/B</td>
</tr>
<tr>
<td>Assess all patients preoperatively to determine whether risk of bleeding complications is standard or high</td>
<td>III/C</td>
</tr>
<tr>
<td>Consider use of vena cava filter in patients who have contraindications to anticoagulation</td>
<td>V/C</td>
</tr>
<tr>
<td>Consider intraoperative and/or immediate postoperative mechanical compression</td>
<td>III/B</td>
</tr>
<tr>
<td>Consider regional anesthesia for the procedure (in consultation with anesthesiologist)</td>
<td>IV/C</td>
</tr>
<tr>
<td>Consider continued use of mechanical prophylaxis postoperatively</td>
<td>IV/C</td>
</tr>
<tr>
<td>Rapid patient mobilization</td>
<td>V/C</td>
</tr>
<tr>
<td>Routine screening for thromboembolism is not recommended</td>
<td>III/B</td>
</tr>
<tr>
<td>Educate patient about symptoms of thromboembolism after discharge</td>
<td>V/B</td>
</tr>
</tbody>
</table>

lated to a blood or tissue event. An algorithm of blood management was developed based on anticipated blood loss in patients undergoing total hip and total knee arthroplasty. When the algorithm was followed the transfusion rate with allogeneic blood was 2.1%, which was significantly lower \( P < 0.001 \) than a transfusion rate of 16.4% when the algorithm was not followed (Figure 1).

### Preoperative Blood Management

It has been reported in patients undergoing lower extremity joint arthroplasty that if the preoperative hemoglobin level was less than 13 g/dL, the risk of requiring an allogeneic blood transfusion was four times greater compared with a hemoglobin level of 13 to 15 g/dL and was 15.3 times greater compared to patients with a preoperative hemoglobin level of greater than 15 g/dL.18 These data indicate that preoperative hemoglobin levels can be used to dictate the need for different blood management strategies. It has been recommended that preoperative anemia be corrected with oral iron supplementation. Preoperative medical conditions can influence risks, including the need for transfusions. A 2009 study found that uncontrolled diabetes mellitus, whether type I or type II, was significantly associated with additional surgical and systemic complications including postoperative hematoma, transfusion risk, and infections following lower extremity total joint arthroplasty. Patient-specific factors such as age, sex, whether or not the patient was hypertensive, and body mass index were evaluated.21 The authors found that when a patient had two or more of these factors, there was a significantly increased risk of allogeneic blood transfusion \( P < 0.02 \).

### Autologous Donation

A snapshot assessment of 9,482 patients undergoing lower extremity total joint arthroplasties was performed and the then-current blood usage was described. Sixty-one percent of patients predonated autologous blood. However, 45% of the predonated autologous blood was not used. Nine percent of patients required allogeneic blood despite predonated autologous blood. For each unit of donated blood, the hemoglobin level is decreased approximately 1.2 to 1.5 g/dL. Autologous donation is an option that the surgeon should consider for the patient, bearing in mind concerns regarding wasted donated units and the resultant associated preoperative decrease in hemoglobin.

### Donor-Directed Donation

The risk of hepatitis B and C transmission as well as the risk of human immunodeficiency virus (HIV) transmission is increased in patients who received donor-directed donations as opposed to autologous blood. This increased risk is possibly because directed donations are from family members or friends who often may be reluctant to disclose risk factors for viruses such as hepatitis and/or HIV. Donor-directed donation is rarely used because of these concerns.

Erythropoietin is effective for rapidly increasing the hemoglobin level and is indicated for patients with a hemoglobin level of 10 to 13 g/dL. Further, erythropoietin is an important component of the blood conservation algorithm shown in Figure 1; in that study, patients who followed the algorithm and were given erythropoietin if the anticipated hemoglobin was below a certain level had a reduced need for blood transfusion following total hip and total knee arthroplasty.
Intraoperative Blood Management

Methods for intraoperative blood management include effective anesthetic techniques, intraoperative blood salvage, acute normovolemic hemodilution, the use of antifibrinolytic agents, the use of a bipolar ceiling device, perioperative injections, and topical agents. Patients undergoing total knee arthroplasty were compared using a computer-assisted minimally invasive technique with a standard technique in a prospective randomized study. The authors found that despite increased duration of surgery, patients treated with the computer-assisted minimally invasive technique had a decreased length of hospital stay and decreased blood loss.

A meta-analysis of the use of antifibrinolytic agents in spine surgery found that aprotinin, tranexamic acid, and epsilon-aminocaproic acid were effective in reducing blood loss and transfusions. These agents were particularly effective in patients undergoing correction of spinal deformities and in patients with long arthrodesis constructs. However, at the present time, these agents are not approved by the United States Food and Drug Administration for these indications. The use of tranexamic acid in patients undergoing total hip replacement was evaluated in a 2009 study. Intravenous administration of 1 g of tranexamic acid during induction resulted in decreased early postoperative blood loss and total blood loss, but intraoperative blood loss was not affected. Tranexamic acid acts during the early phase of the fibrinolytic cascade. Concerns about the use of antifibrinolytic agents include an increased risk of thrombosis; however, an increased incidence of deep venous thrombosis was not found. Concern has also been expressed about the cost of these agents; however, tranexamic acid was cost-effective in reducing blood loss and transfusion requirements after total hip replacement, especially in women, in the 2009 study.

Topical agents such as a fibrin sealant have been studied in patients undergoing total knee arthroplasty. According to results from a prospective randomized trial, the use of the fibrin sealant safely decreased blood drainage while maintaining higher hemoglobin levels. Fibrin sealant should be considered as part of a blood management strategy, particularly in patients undergoing total knee arthroplasty and especially in those who have an inflamed synovium.

Postoperative Blood Management

Patients undergoing total hip and total knee replacement who preoperatively had mild anemia and hemoglobin levels ranging from 10 to 13 g/dL were studied. Treatment of patients with preoperative erythropoietin injections was found to be more effective but more costly in reducing the need for allogeneic red blood cell transfusions.
blood transfusion in mildly anemic patients than the use of postoperative reinfusion of autologous shed blood. In a randomized controlled trial of patients undergoing total knee replacement, the use of autologous retransfusion was evaluated.\textsuperscript{28} No adverse reactions associated with retransfusion of autologous blood were found. This study confirmed the safety of reinfusion of postoperative autologous shed blood. In a randomized controlled trial of patients undergoing total knee arthroplasty but casts doubt regarding their efficacy in reducing the need for allogeneic transfusion compared with standard suction drainage after total knee arthroplasty.

The use of allogeneic blood transfusion is part of the strategy for blood management, and it is an option that should be considered. Allogeneic blood is currently safer than ever before because blood can be screened for various viruses. However, a risk of viral transmission as well as bacterial contamination of the blood exists but has greatly decreased. In 1984 the risk of HIV transmission was greater than 1 per 1,000, and in 2001 it was less than 1 per 1 million.\textsuperscript{29} Further, administrative errors persist.\textsuperscript{19}

### Summary

Coagulation, thromboembolism, and blood management are important topics related to patient management, particularly for those patients undergoing total hip or total knee arthroplasty. The AAOS clinical guideline on the prevention of symptomatic pulmonary embolism in these patients is based on a systematic review of the literature and is evidence based. This guideline provides useful information related to patient management regarding pulmonary embolism prophylaxis. In addition, ACCP provides evidence-based guidelines, which include deep venous thrombosis and pulmonary embolism. Prevention of deep venous thrombosis is important; however, orthopaedic surgeons are most concerned with prevention of pulmonary embolism, which can be fatal. A patient-specific plan for blood management should be developed based on factors including preoperative hemoglobin level and anticipated blood loss of the proposed surgical intervention. Patients undergoing a particularly difficult revision will more urgently need multiple blood management strategies than the patient undergoing an anticipated straightforward unilateral primary joint arthroplasty.

### Annotated References


3. Galton DD, McGovern SC, Hanssen AD, Larson DR, Harrington JR, Clarke HD: Early return to surgery for evacuation of a postoperative hematoma after primary total knee arthroplasty. J Bone Joint Surg Am 2008;90(11):2331-2336. The authors found that patients who returned to the operating room within 30 days following a primary total knee arthroplasty for evacuation of a hematoma were at significantly increased risk for the development of deep infection and are undergoing subsequent major surgery.


8. Burnett RS, Clohisy JC, Wright RW, et al: Failure of the American College of Chest Physicians-1A protocol for lovenox in clinical outcomes for thromboembolic prophylaxis. J Arthroplasty 2007;22(3):317-324. The authors compared their results of prophylaxis following an ACCP 1A protocol using Lovenox and found that returning to the operating room for wound complications occurred three times more frequently with the use of Lovenox than a previous study using warfarin.


This paper considers the various strategies available for the management of blood loss in patients undergoing orthopaedic and trauma surgery.


Regardless of diabetes type, patients with uncontrolled diabetes mellitus exhibited significantly increased odds of surgical and systemic complications including postoperative hemorrhage during their index hospitalization following lower extremity total joint arthroplasty.


The authors found there was less blood loss and no increase in the rate of short-term complications in the group undergoing computer-assisted, minimally invasive total knee arthroplasty compared with standard total knee arthroplasty.


The authors performed a meta-analysis of antifibrinolytic agents in spine surgery and found that they were effective for reducing blood loss in transfusions. The use of these agents, which include aprotinin, tranexamic acid, and epsilon-aminocaproic acid, is not an FDA approved indication for these agents.


The authors found that a preoperative bolus of 1 g of tranexamic acid was cost-effective in reducing blood loss in transfusion requirements after total hip replace-
ment especially in women. The results suggest that fibrin sealant can safely reduce blood drainage following total knee arthroplasty while maintaining higher hemoglobin levels.


Preoperative epoetin injections were more effective but more costly in reducing the need for allogeneic blood transfusions in mildly anemic patients who had postoperative retransfusion of autologous blood.


The authors concluded the cost-effectiveness and continued use of autologous drains in total knee replacement should be questioned.


This article reports that levels of allogenic blood transfusion-transmitted virus in the United States are exceedingly low.