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CURRENT CONCEPTS REVIEW

PREVENTION OF VENOUS THROMBOEMBOLIC DISEASE AFTER TOTAL HIP AND KNEE ARTHROPLASTY

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- ▶ Patients undergoing total hip and knee arthroplasty are at increased risk for the development of venous thromboembolic disease, and there is general agreement that these patients require prophylaxis.
- ▶ The selection of a prophylactic agent involves a balance between efficacy and safety and often needs to be individualized for specific patients and institutions.
- ▶ Despite extensive research, the ideal agent for prophylaxis against deep venous thrombosis has not been identified. The results of randomized trials indicate that low-molecular-weight heparin, warfarin, and fondaparinux are the most effective prophylactic agents after total hip arthroplasty and that low-molecular-weight heparin, warfarin, fondaparinux, and pneumatic compression boots are the most effective agents after total knee arthroplasty.
- ▶ The duration of prophylaxis against deep venous thrombosis after total hip and knee arthroplasty remains controversial. Prophylaxis should be continued beyond hospital discharge. In the future, the determination of the duration of prophylaxis will be based on the risk stratification of individual patients.
- ▶ The practice of discharging patients from the hospital without prophylaxis, even when the decision is based on negative results of procedures that screen for the presence of deep venous thrombosis, is not cost-effective.

Total hip and knee arthroplasties are extremely successful orthopaedic procedures that relieve pain, improve function, and enhance the quality of patients' lives. However, these procedures are also associated with a risk of morbidity and mortality from the development of venous thromboembolic disease. In addition, because the number of total joint arthroplasties has increased to more than 600,000 annually¹, it is essential that an effective method of prophylaxis be selected for patients undergoing these operations.

In North America, there is general agreement that prophylaxis against deep vein thrombosis is necessary after total joint arthroplasty, but the ideal prophylactic regimen has not been identified. The selection of a prophylactic regimen involves a balance between efficacy and safety. Surgeons are particularly concerned about bleeding because it can lead to hematoma formation, infection, a reoperation, and a prolonged hospital stay. The selection of a prophylactic agent is also influenced by the more frequent use of regional anesthesia; the recent development of perioperative pain protocols involv-

ing the use of anti-inflammatory medications, which can also increase the risk of bleeding complications; and the continued decrease in the duration of hospital stays. Over the past decade, a number of agents have been found to provide safe and effective prophylaxis in randomized clinical trials. However, areas of controversy include the timing of the prophylaxis after the operative procedure, the duration of the prophylaxis, and the efficacy of screening for deep vein thrombosis after total joint arthroplasty. The purpose of this review is to provide a critical analysis of the different prophylactic options and to address the aforementioned controversial issues for patients undergoing total hip or knee arthroplasty.

Pathogenesis

The formation of thrombi is associated with Virchow's triad of venous stasis, endothelial injury, and hypercoagulability². This triad has been found to occur during the perioperative period in patients treated with total hip or knee arthroplasty. Venous stasis may occur secondary to the positioning of the

limb during the procedure, localized postoperative swelling, and a decreased activity level after the operation^{3,5}. A dramatic reduction in the venous capacitance of the lower extremity and in venous outflow has been demonstrated during hip arthroplasty⁶, and this may be exacerbated during dislocation of the hip and insertion of the femoral prosthesis. In addition, total knee arthroplasty is usually performed with a tourniquet on the thigh and with the knee in a flexed and subluxated position, which can increase the propensity for clot formation. The endothelium may be injured during positioning and manipulation of the extremity, and it may sustain a thermal injury from bone cement^{3,7,8}. Tissue thromboplastin and other clotting factors are released during the course of the operative procedure, and they can aggregate in regions of venous stasis. A relative hypercoagulable state can develop during the procedure because the blood loss can result in reduction in antithrombin III and inhibition of the endogenous fibrinolytic system, which further promote thrombus propagation^{8,12}.

Sharrock et al. studied circulating markers of thrombin generation and fibrinolysis during different aspects of a total hip arthroplasty to define exactly when the thrombogenic stimulus reached its peak¹³. All of the procedures were performed with the patient under hypotensive epidural anesthesia. The levels of multiple markers of thrombin generation, including prothrombin F1.2, thrombin-antithrombin, fibrinopeptide A, and D-dimer, were markedly increased during preparation of the femoral canal and insertion of the femoral component. The levels of these thrombogenic markers were minimally influenced by preparation of the acetabulum. It has been hypothesized that manipulation of the femoral canal leads to release of thromboplastin in the bone marrow or fat, which causes a thrombogenic stimulus^{3,13}.

Sharrock et al. also studied circulatory indices of thrombosis and fibrinolysis following knee arthroplasty¹⁴. Increases in levels of D-dimer, fibrinopeptide, and thrombin-antithrombin complexes were noted following tourniquet deflation. Manipulation of the femoral canal with placement of an intramedul-

lary device to prepare for the insertion of the femoral or tibial component may also be a thrombogenic stimulus, but this has not yet been studied to our knowledge. Maynard et al. used serial contrast venography to evaluate the development of venous thrombi after unilateral total knee arthroplasty¹⁵. Twenty-four hours after the procedure, they found a distal deep vein thrombus in 45% (nineteen) of forty-two legs and a popliteal thrombus in 5% (two) of forty-one lower extremities. The findings of these three studies suggest that venous thromboembolic disease begins during the perioperative period, which means that the goal of prophylaxis is not to prevent clot formation but to prevent thrombus propagation¹⁶.

Epidemiology

A number of risk factors for the development of deep venous thrombosis have been identified (Table I)¹⁷. However, even without underlying risk factors, patients who undergo total joint arthroplasty are at high risk for the development of venous thromboembolism^{16,18}. Without either mechanical or pharmacologic prophylaxis, asymptomatic deep venous thrombosis will develop after 40% to 60% of total hip and knee arthroplasties⁹. Proximal deep vein thrombosis will develop after 15% to 25%, and a fatal pulmonary embolism will develop after 0.5% to 2%^{10-12,16,18,19-22}. Pulmonary embolism is the most common cause of death after total joint arthroplasty when thromboprophylaxis is not used²³. Symptomatic and fatal pulmonary emboli are more common after total hip arthroplasty than after total knee arthroplasty⁹.

Pellegrini et al.²⁴ reported that a symptomatic pulmonary embolism developed in four (17%) of twenty-three patients with an untreated calf-vein thrombosis. This study and those mentioned above suggest that patients with a distal deep venous thrombosis after total joint arthroplasty are at increased risk for proximal clot propagation and should be either treated with anticoagulation or followed closely with serial duplex scans to delineate proximal clot migration. Although both proximal and distal clots form in patients who

TABLE I Risk Factors for Venous Thromboembolic Disease

Clinical Risk Factors	Hemostatic Abnormalities (Hypercoagulable States)
Advanced age	Antithrombin-III deficiency
Fracture of the pelvis, hip, femur, or tibia	Protein-C deficiency
Paralysis or prolonged immobility	Protein-S deficiency
Prior venous thromboembolic disease	Dysfibrinogenemia
Operation involving abdomen, pelvis, or lower extremities	Lupus anticoagulant and antiphospholipid antibodies
Obesity	Myeloproliferative disorder
Congestive heart failure	Heparin-induced thrombocytopenia
Myocardial infarction	Disorders of plasminogen and plasminogen activation
Stroke	

*Adapted with permission from: Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I9-I16.

have had a total joint arthroplasty, most of these thrombi resolve spontaneously and do not definitively increase the risk of venous stasis disease²⁵.

Since the duration of hospital stays has decreased, the occurrence of deep venous thrombosis after hospital discharge has increased. In a study of 19,586 hip and 24,059 knee arthroplasties performed between 1991 and 1993 in California²⁶, White et al. determined that, although the cumulative incidence of symptomatic deep vein thrombosis was low (developing after 2.8% [556] of the total hip arthroplasties and after 2.1% [508] of the total knee arthroplasties), a majority of the events (76% of those following total hip arthroplasty and 47% of those following total knee arthroplasty) occurred after hospital discharge. Most patients (88%) received either warfarin or low-molecular-weight heparin for chemoprophylaxis; the average duration of prophylaxis with warfarin was four weeks, but the average duration of prophylaxis with low-molecular-weight heparin was not reported. The median time until diagnosis of a symptomatic deep venous thrombosis was seventeen days after total hip arthroplasty and seven days after total knee replacement. These results suggest a slower development of deep venous thrombosis following total hip arthroplasty and that perhaps the duration of prophylaxis should be different for these two procedures. Finally, symptomatic clots develop in some patients despite adequate prophylaxis.

The relationship between thrombophilia associated with genetic diseases and the risk of deep venous thrombosis after total joint arthroplasty requires further study. Factor-V Leiden mutation (activated protein-C resistance), antiphospholipid antibody syndrome, protein-C and S deficiency, and impairment of the fibrinolytic system potentially increase the risk of symptomatic venous thromboembolic disease developing after arthroplasty in some patients²⁷⁻²⁹. Higher rates of symptomatic deep venous thrombosis have been noted in patients with factor-V Leiden mutation, prothrombin mutations, and genetic abnormalities related to antithrombin III²⁷⁻³². However, routine preoperative screening for gene mutations has not been recommended because the overall rate of thrombophilic disorders is low and the risk of symptomatic deep venous thrombosis is not markedly increased in patients who have these disorders. Risk stratification of patients on the basis of genetic coagulation profiles would allow the development of different types of prophylactic regimens. This could reduce the number of complications associated with chemoprophylaxis as well as be more cost-effective.

Prophylaxis Following Total Hip Arthroplasty

Both pharmacologic and mechanical approaches have been used to decrease the risk of venous thromboembolism after total hip arthroplasty. The pharmacologic agents presently include warfarin, standard heparin, low-molecular-weight heparin, fondaparinux, and aspirin. Mechanical devices include compression stockings, sequential intermittent pneumatic compression boots, and intermittent plantar compression. All studies included in this analysis were randomized clinical tri-

als in which either venographic findings or symptomatic venous thromboembolic disease was used as a surrogate outcome measure to determine efficacy.

Pharmacologic Methods

Warfarin

For more than forty years, warfarin has been successfully used as a prophylactic agent following hip surgery^{11,33-37}. Warfarin exerts its anticoagulant effect by inhibiting the hepatic production of vitamin K-dependent clotting factors II, VII, IX, and X³⁸. Warfarin has been shown to decrease the prevalence of deep venous thrombosis by approximately 60% and the prevalence of proximal venous thrombosis by 70% when compared with prevalences in patients not treated with prophylaxis¹⁸.

Warfarin is administered orally and is less expensive than other anticoagulants³⁹. However, use of warfarin has several drawbacks. First, regular monitoring of the international normalized ratio or prothrombin time is necessary. Second, warfarin has a delayed onset of action and may leave patients relatively unprotected during the early postoperative period¹⁶. Therefore, it is strongly recommended that warfarin be continued after hospital discharge to limit clot propagation and the development of symptomatic pulmonary embolism. Third, warfarin has been associated with a 1% to 5% occurrence of major postoperative bleeding³⁹⁻⁴². Some surgeons try to avoid attaining the target international normalized ratio of 2.0 in order to reduce bleeding or to avoid the inconvenience of postoperative monitoring, but this strategy increases the risk of deep venous thrombosis⁴³. Finally, warfarin also interacts with numerous medications as a result of its metabolism in the cytochrome P450 system in the liver. The combination of warfarin and nonsteroidal anti-inflammatory agents has been shown to increase the risk of hemorrhagic peptic ulcer by nearly thirteenfold in elderly patients⁴⁴. Even patients who take cyclooxygenase-2 (COX-2) inhibitors are still at risk for gastrointestinal bleeding. Recently, a number of COX-2 inhibitors have been removed from the market because of an increased risk of cardiovascular events^{45,46}.

The efficacy of warfarin as a prophylactic agent following total hip arthroplasty has been assessed in both cohort studies and randomized clinical trials over the past four decades^{41,47-50}. A meta-analysis of all randomized, controlled trials published from 1966 through 1998 included fifty-two studies involving a total of 10,929 patients treated with total hip arthroplasty⁵¹. Patients treated with warfarin had the lowest rate of proximal deep venous thrombosis (6.3%) as well as the lowest rate of symptomatic pulmonary embolism (0.16%). The risk of major postoperative bleeding episodes in patients taking warfarin was no higher than that in patients treated with a placebo⁵¹.

Warfarin was compared with different low-molecular-weight heparins in four recent multicenter randomized trials in which the results of venography were used as a surrogate outcome measure^{41,47-50}. Overall, the four studies revealed significantly lower rates of deep venous thrombosis in patients treated with low-molecular-weight heparin (12.7% [331] of

TABLE II Summary of Results from Multiple Randomized Clinical Trials Comparing Warfarin with Low-Molecular-Weight Heparin After Total Hip Arthroplasty

Study	No. of Patients	No. with Successful Venography	Overall Rate of Deep Venous Thrombosis (%)	Rate of Proximal Deep Venous Thrombosis (%)	Rate of Pulmonary Embolism* (%)	Rate of Bleeding Episodes (%)
Hull et al. ⁴⁸						
Warfarin	388	363	10.7	1.0	NA	4.2
Fragmin (dalteparin)	388	354	24	3.0	NA	5.1
Hamulyak et al. ⁶⁶						
Warfarin	342	257	20.0	5.8	NA	2.8
Nadroparine	330	260	17.0	6.5	NA	1.5
RD Heparin Arthroplasty Group ⁵⁰						
Warfarin	218	174	11.0	6.0	0	4.0
RD heparin	211	178	7.0	3.0	0	4.0
Francis et al. ⁶⁵						
Warfarin	279	190	26.0	8.0	NA	1.0
Dalteparin	271	192	15.0	5.0	NA	4.0

*NA = not available.

2605 patients, with a range of 3% to 31% among the studies) compared with patients treated with warfarin (16.9% [443] of 2621 patients, with a range of 3% to 37%). In general, the bleeding rates were higher in patients who were treated with low-molecular-weight heparin^{41,47-50}. The results of these studies will be discussed in more detail when we review the low-molecular-weight heparins (Table II).

Warfarin prophylaxis is usually initiated with a 5 or 10-mg dose on the evening before the operation or a 10-mg dose on the evening after the operation. Subsequent doses are determined by measurement of the international normalized ratio, which represents the prothrombin time ratio that would have been obtained if the international reference thromboplastin had been used instead of the local reagent. The target international normalized ratio for prophylaxis after total joint arthroplasty is between 1.8 and 2.5⁸.

Warfarin remains a safe and effective agent for prophylaxis following hip arthroplasty (Table III). Although warfarin does not appear to be quite as effective as low-molecular-weight heparin for preventing venous thromboembolic disease, there is a decreased risk of bleeding complications. Large randomized clinical trials are needed to compare warfarin with other treatment modalities.

Standard Heparin

Standard unfractionated heparin is a heterogeneous mixture of glycosaminoglycans. The major anticoagulant effect of heparin is due to the high binding affinity for a unique pentasaccharide and antithrombin III. The interaction of heparin with antithrombin III accelerates the ability of heparin to inhibit thrombin, factor IX, and factor Xa (Fig. 1). In order to inhibit thrombus formation, heparin must bind to both thrombin and antithrombin III simultaneously. Therefore, a minimum

18-saccharide chain length is required for ternary complex formation⁵²⁻⁵⁴.

Standard low-dose heparin (5000 units administered subcutaneously twice daily) is not currently recommended for the prevention of proximal deep-vein thrombosis after total hip arthroplasty^{20,55-57}. Adjusted-dose heparin has been shown to be effective in limiting clot formation after total hip arthroplasty, but daily monitoring of the activated partial thromboplastin time is necessary^{5,27,58,59}. For this reason and because multiple subcutaneous injections are required, adjusted-dose heparin never became popular in North America.

Low-Molecular-Weight Heparin

The low-molecular-weight heparins are relatively homogeneous in size, with molecular weights between 1000 and 10,000 Da, and are prepared by either chemical or enzymatic depolymerization of unfractionated heparin⁵²⁻⁵⁴. The antithrombotic activity of low-molecular-weight heparin is primarily mediated through the inhibition of factor Xa. Since a minimum chain length of 18 saccharides is required for ternary complex formation (heparin-antithrombin III-thrombin), low-molecular-weight heparins can inhibit factor Xa but not thrombin (Fig. 1)⁵²⁻⁵⁴.

The low-molecular-weight heparins offer several advantages compared with standard heparin. They have better bioavailability (90% compared with 30% to 40% for standard heparin); reduced binding to plasma proteins, vascular endothelium, and circulating cells; and a prolonged circulating half-life compared with standard heparin⁶⁰. These biologic properties lead to a more consistent biologic effect among patients of different weights. A fixed dose of low-molecular-weight heparin can be used, and there is no need for laboratory monitoring. Prophylactic doses of low-molecular-weight

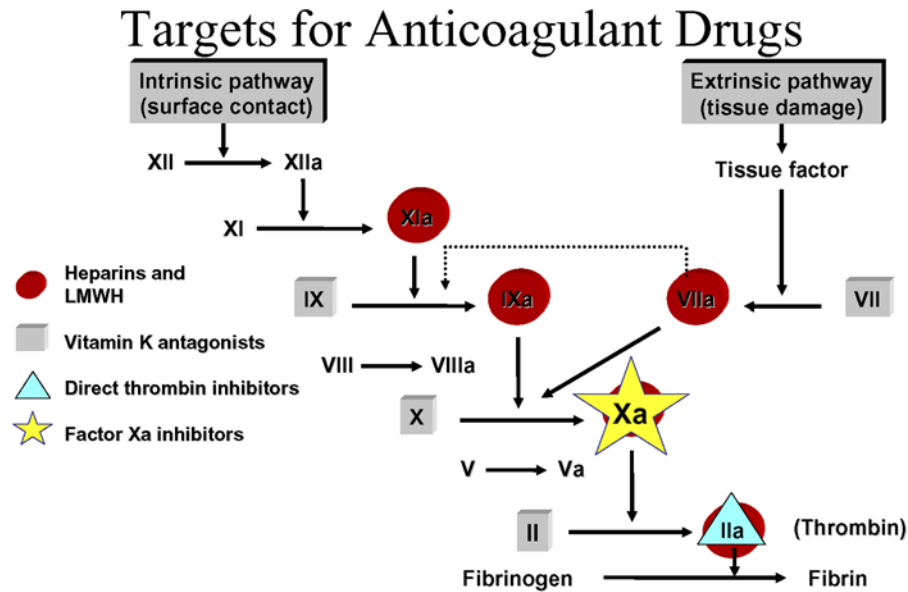


Fig. 1
Targets for anticoagulant drugs. LMWH = low-molecular-weight heparin. (Reproduced, with modification, from: Petitou M, Lormeau JC, Choay J. Chemical synthesis of glycosaminoglycans: new approaches to antithrombotic drugs. *Nature*. 1991;350(6319 Suppl):30-3. Reprinted with permission.)

heparin do not increase the activated partial thromboplastin time⁵⁴. The low-molecular-weight heparins are metabolized in the kidney and therefore should be used with caution in patients with renal insufficiency. Originally, it was thought that low-molecular-weight heparin was not associated with the development of thrombocytopenia, but this is not true⁶¹. It has been suggested that the platelet count of patients who are receiving low-molecular-weight heparin for prophylaxis against deep venous thrombosis be checked at least once prior to discharge.

The low-molecular-weight heparins, as a class of drugs, have been shown to reduce the risk of proximal and distal deep-vein thrombosis by at least 70% compared with the risk in patients treated with a placebo^{18,44,62-64}. As stated previously, the low-molecular-weight heparins have been compared with warfarin in a number of multicenter randomized clinical trials in which the results of venography were used as a surrogate outcome measure (Table II)^{48,50,51,65,66}. A review of these studies revealed that different low-molecular-weight heparins were more efficacious than warfarin for limiting clot formation, but the bleeding rates associated with low-molecular-weight heparins are higher than those associated with warfarin.

Hull et al. performed a multicenter randomized trial not only to compare the low-molecular-weight heparin dalteparin with warfarin but also to determine the influence of the timing of the administration of the heparin on efficacy and safety³⁸. Patients were treated with warfarin (10 mg) started on the evening after the surgery followed by daily doses to maintain an international normalized ratio between 2.0 and 3.0, or they were given a half dose of dalteparin (2500 IU) four hours after the surgery and then the standard (5000-IU) dose begin-

ning on the first postoperative day. All patients received anticoagulation for thirty-five days after the surgical procedure and were evaluated with venograms between four and eight days after the total hip arthroplasty and then again at thirty-five days after the arthroplasty. The overall rate of deep venous thrombosis was significantly higher ($p < 0.001$) in the warfarin group (sixty-nine of 188; 36.7%) than in the dalteparin group (sixty-eight of 345; 19.7%). The rate of proximal clot formation was 2.0% (three of 151) in the dalteparin group and 9.2% (fourteen of 153) in the warfarin group ($p = 0.007$). The rate of bleeding episodes was significantly higher ($p = 0.02$) in the dalteparin group (twenty-eight of 487; 5.7%) than in the warfarin group (twenty of 489; 4.1%). However, no major bleeding episodes were reported in either group. The results of this study suggest that a modified low-molecular-weight-heparin regimen in which prophylaxis is started soon after the procedure significantly reduces both the total rate of deep venous thrombosis and the rate of proximal deep venous thrombosis but is associated with a higher risk of bleeding. The question is: does giving a half-dose of the drug in the early postoperative period increase its efficacy? This issue requires further study.

In most randomized trials, venographic findings and asymptomatic clot formation have been used as surrogate outcomes to determine the efficacy of different prophylactic agents. There is some concern regarding the clinical relevance of these trials. Therefore, Colwell et al. performed a multicenter randomized clinical trial to evaluate the efficacy of enoxaparin and warfarin in preventing symptomatic deep venous thrombosis and pulmonary embolism after total hip

arthroplasty⁴⁷. Patients were randomly assigned to receive either enoxaparin twice daily beginning on the morning after the operative procedure or warfarin beginning on the night of the total hip arthroplasty. Patients received prophylaxis for an average of seven days. The rate of in-hospital symptomatic venous thromboembolic events was significantly higher ($p < 0.01$) in patients who received warfarin prophylaxis (seventeen of 1495; 1.1%) than in those who received enoxaparin (four of 1516; 0.3%). However, there was no difference in the rates of post-discharge symptomatic venous thromboembolism between the warfarin group (fifty-five of 1495; 3.7%) and the low-molecular-weight-heparin group (fifty-five of 1516; 3.6%). Major bleeding episodes were significantly more frequent ($p < 0.05$) in the enoxaparin group (eighteen of 1516; 1.2%) than in the warfarin group (eight of 1495; 0.5%). The results of this study demonstrated that enoxaparin is more effective than warfarin in preventing symptomatic venous thromboembolic events in the hospital, but there was no difference in the rates of post-discharge deep venous thrombosis. The rate of major bleeding episodes was increased in patients receiving low-molecular-weight heparin.

The data from these randomized trials demonstrate that low-molecular-weight heparins are more effective than warfarin in limiting the development of deep venous thrombosis. However, there appears to be an increased risk of postoperative bleeding episodes with low-molecular-weight heparins. The dosing regimens of the two most popular low-molecular-weight heparins used in North America, enoxaparin and dalteparin, are different. It is recommended that the initial dose of enoxaparin be administered twelve to twenty-four hours after the end of the surgical procedure. Administration of enoxaparin less than twelve hours after the surgical procedure increases the risk of bleeding^{67,68}. In contrast, a half-dose of

dalteparin is administered four hours after the operative procedure, followed by a full dose on the first postoperative day. The efficacy of these agents has not been compared in randomized trials, to our knowledge. Overall, the low-molecular-weight heparins are safe and effective agents for limiting the incidence of thromboembolic disease following total hip arthroplasty (Table III).

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that acts as a specific inhibitor of factor Xa with no direct inhibition of thrombin⁶⁹⁻⁷¹. The antithrombotic activity of fondaparinux is due to its selective binding to antithrombin III, which causes an irreversible conformational change at the binding site for factor Xa (Fig. 2). Fondaparinux has no influence on platelet activity, and it does not enhance fibrinolytic activity. Fondaparinux has received the approval of the United States Food and Drug administration for prophylaxis for patients treated with total hip or knee arthroplasty or for a hip fracture⁷²⁻⁷⁴.

Two large clinical trials have demonstrated the efficacy of fondaparinux as a prophylactic agent in patients treated with total hip arthroplasty^{75,76}. Turpie et al.⁷⁶ performed a randomized, double-blind, multicenter trial to evaluate the efficacy of fondaparinux and enoxaparin in 2275 consecutive patients who had undergone elective total hip arthroplasty. The first dose of fondaparinux was administered six hours following the surgery, and the first dose of low-molecular-weight heparin was given twelve hours following the surgery. The patients in both groups received prophylaxis against deep venous thrombosis for an average of seven days. There was no significant difference ($p = 0.099$) between the two groups with regard to the overall rates of deep venous thrombosis (forty-four [5.6%] of 784 in the fondaparinux group and sixty-five

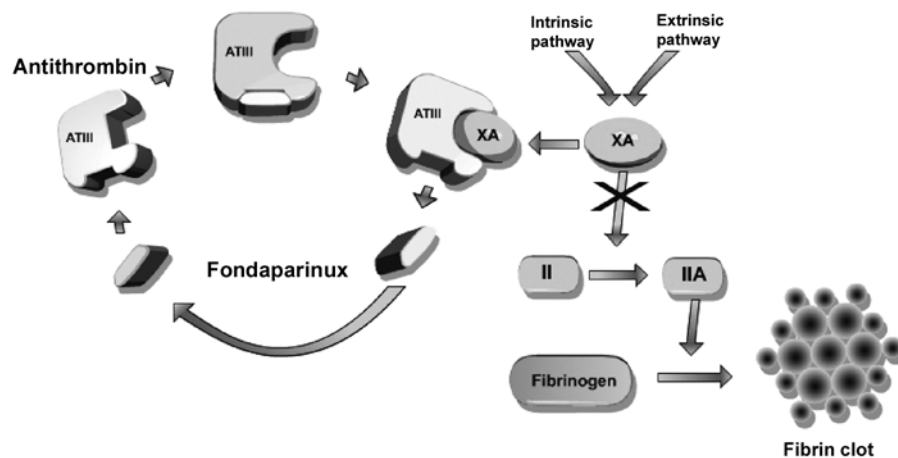


Fig. 2

Mechanism of action of fondaparinux. Fondaparinux binds to antithrombin III (ATIII), causing a conformational change in the binding site for factor Xa. Factor Xa selectively binds to ATIII-fondaparinux and is subsequently degraded, thus decreasing the formation of factor Iia and fibrin clot formation. (Reprinted, with permission, from: Feeley BT, Hsu WK, Lieberman JR. Thromboprophylaxis in hip fractures. *Tech Orthop*. 2004;19:171-80.)

[8.2%] of 796 in the enoxaparin group). In addition, there was no difference in the rates of proximal clots (fourteen [1.7%] of 816 and ten [1.2%] of 830, respectively; $p = 0.42$) or in the rates of symptomatic pulmonary embolism (0.4% and 0.1%, respectively)⁷⁶. The rates of major bleeding episodes were also similar in the two groups (twenty [1.8%] of 1128 and eleven [0.10%] of 1129; $p = 0.11$)⁷⁶.

The two major side effects associated with fondaparinux are bleeding and thrombocytopenia. The risk of a major bleeding episode was increased if the first dose of fondaparinux was administered within six hours after the operation; however, this difference was not significant ($p = 0.11$)⁷⁵. Moderate thrombocytopenia (50,000 to 100,000 platelets/mL) was also noted in 2.0% of patients^{76,77}. Since fondaparinux is metabolized in the kidney and excreted in the urine, severe renal impairment (creatinine clearance of <30 mL/min) is a contraindication for its use. Measurements of the hematocrit, platelet counts, and serum creatinine levels at least once prior to discharge are recommended for patients who have been given fondaparinux.

Fondaparinux appears to be as safe and effective as the low-molecular-weight heparins for providing chemoprophylaxis following total hip replacement (Table III). However, there are concerns about bleeding with fondaparinux. A randomized trial is in progress to determine the effect on both safety and efficacy of delaying administration of the drug until the morning after the surgical procedure.

TABLE III Recommendations for Prophylaxis Against Deep Venous Thrombosis After Total Joint Arthroplasty

	Grade of Recommendation*
Total hip arthroplasty	
Warfarin	A
Low-molecular-weight heparin	A
Fondaparinux	A
Aspirin	B
Pneumatic compression boots	I
Intermittent plantar compression	I
Compression stockings	A
Total knee arthroplasty	
Warfarin	A
Low-molecular-weight heparin	A
Fondaparinux	A
Pneumatic compression boots	A
Aspirin	B
Intermittent plantar compression	I

*A = good evidence (Level-I studies with consistent findings) for or against recommending intervention, B = fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention, C = Conflicting or poor-quality evidence (Level-IV or V studies) not allowing a recommendation for or against intervention, and I = there is insufficient evidence to make a recommendation.

Aspirin

Aspirin limits platelet aggregation by inhibiting thromboxane A₂, thereby decreasing thrombus formation. Historically, aspirin has been an attractive chemoprophylactic agent following total hip arthroplasty because it is a simple antiplatelet oral agent that requires no monitoring. Although aspirin does lower the risk of thrombotic complications following total hip arthroplasty compared with the risk associated with a placebo, it is not as effective as either low-molecular-weight heparins or warfarin for preventing deep venous thrombosis⁵¹.

The Pulmonary Embolism Prevention (PEP) trial was a randomized trial performed to assess the efficacy of aspirin in preventing symptomatic venous thromboembolic disease in 4088 patients who had undergone elective total hip arthroplasty⁷⁸. The patients were randomized to receive either aspirin ($n = 2047$) or a placebo ($n = 2041$) for thirty-five days. There was no difference in the rate of symptomatic deep venous thrombosis between the aspirin group (twenty-two of 2047; 1.1%) and the placebo group (twenty-six of 2041; 1.3%). Eight (0.4%) of the patients in each group had a pulmonary embolus ($p > 0.05$). Sixteen patients (0.8%) in the aspirin group and eight (0.4%) in the placebo group required evacuation of a hematoma; however, this difference was not significant ($p = 0.1$). Aspirin did not reduce the risk of symptomatic deep venous thrombosis following elective hip arthroplasties. A major weakness of the PEP trial was that there were numerous protocol violations in both groups (12% of the patients received non-study aspirin or a nonsteroidal anti-inflammatory drug during the study period, and 26% received low-molecular-weight heparin). In addition, the study was not designed to compare aspirin with other effective prophylactic regimens. Therefore, limited conclusions can be drawn regarding the efficacy of aspirin as a prophylactic agent following total hip arthroplasty.

In a recent meta-analysis of the efficacy of different prophylactic regimens, eight studies assessing aspirin as an agent for chemoprophylaxis in a total of 687 patients were identified⁵¹. However, all of the studies were single-center investigations. In addition, in two of the studies, operations were performed with hypotensive epidural anesthesia, which may have a significant impact on the rates of deep venous thrombosis. In the meta-analysis, aspirin therapy was associated with a 19.7% prevalence of distal deep venous thrombosis, an 11.4% prevalence of proximal thrombus formation, and a 1.3% prevalence of symptomatic pulmonary embolism⁵¹. In contrast, the risks with warfarin were 17.1%, 6.3%, and 0.16%, respectively, and the prevalences with low-molecular-weight heparin were 9.6%, 7.7%, and 0.36%, respectively. The rate of distal deep venous thrombosis was lower with low-molecular-weight heparin than with either warfarin ($p = 0.0047$) or aspirin ($p = 0.0005$); however, there were no significant differences among the agents with regard to the rates of proximal deep venous thrombosis and fatal pulmonary embolism⁵¹. In summary, aspirin appears to lower the risk of thrombotic complications following total hip arthroplasty, but it is outperformed by both warfarin and low-molecular-weight

TABLE IV Summary of Results from Multiple Randomized Clinical Trials Comparing Warfarin with Low-Molecular-Weight Heparin After Total Knee Arthroplasty

Study	No. of Patients	No. with Successful Venography	Overall Rate of Deep Venous Thrombosis (%)	Rate of Proximal Deep Venous Thrombosis (%)	Rate of Pulmonary Embolism (%)	Rate of Bleeding Episodes (%)
Hull et al. ⁴⁸						
Warfarin	324	277	54.9	12.3	0	2.4
Logiparin	317	258	45.0	7.8	0	4.4
RD Heparin Arthroplasty Group ⁵⁰						
Warfarin	147	147	41.0	10.0	0	NA
RD heparin	150	150	25.0	6.0	0	NA
Leclerc et al. ⁹⁸						
Warfarin	334	211	51.7	10.4	0.9	1.8
Enoxaparin	336	206	36.9	11.7	0.3	2.1
Heit et al. ⁶⁸						
Warfarin	279	222	38.0	7.0	0.04	4.4
Ardeparin	277	232	27.0	6.0	0	7.9
Fitzgerald et al. ⁹⁶						
Warfarin	176	122	59.0	0.8	0	2.3
Enoxaparin	176	108	38.0	0.0	0	5.2

heparin. To our knowledge, the combination of aspirin and mechanical devices has not been evaluated in multicenter randomized trials and has not been compared with warfarin or low-molecular-weight heparin (Table III).

Mechanical Methods

Pneumatic Compression Boots

Pneumatic compression boots reduce stasis in the lower extremity by increasing the velocity of venous blood flow and by enhancing local endogenous fibrinolytic activity^{79,80}. However, these devices do not affect systemic fibrinolytic activity⁸¹. There are limited data derived from studies of patients treated with total knee arthroplasty⁸² suggesting that mechanical devices that enhance peak venous velocity may be more efficacious than conventional mechanical prophylaxis in reducing overall deep venous thrombosis rates, but carefully designed clinical trials will be necessary to confirm this hypothesis. The advantages of these devices are that no laboratory monitoring is required and there is no risk of bleeding. A major disadvantage is that prophylaxis ceases at the time of discharge. This is an important issue since hospital stays have been reduced to three days or less for many patients. In addition, patients do not receive prophylaxis when the devices are not worn. Authors of recent studies have noted that decreased compliance has a negative impact on efficacy^{83,84}.

A number of randomized trials have demonstrated that pneumatic compression boots can limit distal thrombus formation, but there are questions regarding their ability to reduce rates of proximal clot formation following total hip arthroplasty^{58,59,85-88}. It is difficult to use the available data to assess the true efficacy of these devices for a number of reasons.

First, pneumatic compression boots have not been studied as extensively as pharmacologic agents such as the low-molecular-weight heparins, warfarin, or fondaparinux. Second, the published trials have involved only a single center or a prospective case series, and methods other than venography have been used to measure outcome^{82,87-89}. Thus, although low clot rates have been reported in these series, it is difficult to compare those results with the findings in randomized trials based strictly on venograms. The United States Food and Drug Administration still requires manufacturers to use venograms as a surrogate outcome measure when assessing the efficacy of a prophylactic regimen. Third, many of these trials did not have adequate statistical power with respect to the number of patients enrolled, which limited the quality of the data that were obtained³⁷. Fourth, in a number of studies, pneumatic compression boots were compared with aspirin only rather than with warfarin or a low-molecular-weight heparin^{37,89}.

Three small randomized trials comparing the efficacy of warfarin with that of pneumatic compression boots demonstrated a substantial difference in the rates of proximal clots following total hip arthroplasty, which ranged from 0% to 3% in 217 patients treated with warfarin and from 4% to 12% in 217 patients treated with pneumatic compression boots alone⁸⁵⁻⁸⁷. The data from the aforementioned randomized trials raise concern that pneumatic compression devices may be less effective than pharmacologic agents for the prevention of proximal clot formation. Given the risk of a symptomatic pulmonary embolism developing from a proximal venous thrombus, further investigation is required before pneumatic compression boots can be recommended as a sole means of prophylaxis after total hip arthroplasty.

Intermittent Plantar Compression

Intermittent plantar compression of the foot is another form of mechanical prophylaxis. There is a large plantar venous system that is rapidly emptied with compression of the plantar arch during weight-bearing. Pneumatic devices have been developed that mimic the hemodynamic effects that occur during normal walking, which theoretically increases venous return. The advantages are no risk of bleeding and the ability of patients to tolerate these devices better than they do intermittent pneumatic devices that are applied to the whole leg⁹⁰⁻⁹². The disadvantages that were previously described with respect to pneumatic compression boots are also problems with intermittent plantar compression.

Studies comparing intermittent plantar compression with either a placebo or a fixed dose of heparin have demonstrated that use of the mechanical devices decreases overall thrombosis rates following total hip arthroplasty⁹³⁻⁹⁵. Warwick et al. performed a prospective comparison of a foot pump with a low-molecular-weight heparin (enoxaparin) in a consecutive series of 290 patients⁹⁵. The enoxaparin was administered beginning on the morning after the operative procedure and the foot pump was applied in the recovery room. The rate of deep vein thrombosis, which was documented with venography on the sixth, seventh, or eighth postoperative day, was not significantly different ($p = 0.29$) in the patients treated with the foot pump (eighteen of 138; 13%) compared with the patients who used enoxaparin (twenty-four of 136; 18%). Although the data appear promising, intermittent plantar compression cannot be recommended as the sole means of prophylaxis until larger randomized, prospective trials are performed to compare it with low-dose warfarin, low-molecular-weight heparins, or fondaparinux.

Both pneumatic compression boots and intermittent plantar compression may serve as effective adjunctive agents when combined with pharmacologic agents, but this hypothesis has not been tested in randomized trials, to our knowledge. Compression stockings alone do not reduce the risk of thromboembolism acceptably and therefore should not be used as the sole prophylaxis for patients who have had a hip arthroplasty^{18,63}.

Prophylaxis Following Total Knee Arthroplasty

Prophylaxis against deep vein thrombosis is necessary after total knee arthroplasty. The overall rates of deep venous thrombosis are higher after total knee replacement than after total hip arthroplasty, but the rates of symptomatic pulmonary embolism are higher after total hip arthroplasty⁹. Both pharmacologic agents and mechanical devices provide safe and effective prophylaxis after total knee arthroplasty. Bleeding may be of greater consequence in patients who have had a total knee arthroplasty because hematoma formation can lead to a loss of motion and decreased function. In addition, to our knowledge, no studies have demonstrated that prolonged prophylaxis (twenty-eight days or longer) is necessary following total knee arthroplasty.

Pharmacologic Methods

Warfarin

For four decades, low-dose warfarin has been used successfully for prophylaxis against deep vein thrombosis following total knee replacement, and its efficacy has been proven in both cohort studies and well-designed clinical trials^{67,88,96-98}. We are aware of five randomized multicenter clinical trials comparing the efficacy of adjusted-dose warfarin prophylaxis (with a target international normalized ratio of 2.0 to 3.0) and different low-molecular-weight heparins as prophylactic agents (Table IV)^{48,50,68,96,98}. In these trials, the overall rate of asymptomatic deep venous thrombosis ranged from 38% to 59% in patients treated with warfarin compared with 25% to 45% in patients treated with low-molecular-weight heparin. In every study, the low-molecular-weight heparin was more effective than the warfarin prophylaxis, but no study showed a significant difference in the rates of symptomatic proximal deep venous thrombosis or pulmonary embolism. The bleeding rates were generally higher in the patients who received prophylaxis with a low-molecular-weight heparin^{68,96,98}. We are aware of only one small study comparing warfarin prophylaxis with pneumatic compression boots following total knee arthroplasty⁸⁸. Warfarin was noted to be more effective in limiting overall clot formation in that study.

The available data suggest that warfarin is a safe and effective method of prophylaxis after total knee arthroplasty. Although warfarin is not as effective as low-molecular-weight heparins with regard to limiting overall deep venous thrombosis formation, it is associated with decreased bleeding rates.

Low-Molecular-Weight Heparin and Unfractionated Heparin

As stated previously, the low-molecular-weight heparins have been demonstrated to provide effective and safe prophylaxis after total knee arthroplasty in multiple clinical trials. As stated, we found five randomized multicenter clinical trials comparing the efficacy of adjusted-dose warfarin prophylaxis (with a target international normalized ratio of 2.0 to 3.0) with that of different low-molecular-weight heparins as prophylactic agents^{48,50,68,96,98}. Low-molecular-weight heparins were found to be more effective in limiting the formation of asymptomatic clots, but the rates of clinically relevant bleeding were generally higher in patients who received a low-molecular-weight heparin as prophylaxis (Table IV)^{48,50,51,68,96,98}.

In general, standard unfractionated heparin is not used for prophylaxis following total knee arthroplasty because multiple injections and daily monitoring are required^{99,100}.

Fondaparinux

Fondaparinux is injected once a day and has recently been approved by the United States Food and Drug Administration for use in patients treated with total knee arthroplasty. Fondaparinux was recently compared with the low-molecular-weight heparin enoxaparin in a randomized multicenter trial¹⁰¹. The fondaparinux was administered six hours after the operation, and the enoxaparin was given on the morning after

the operation. Fondaparinux was more effective in preventing thrombus formation but was associated with a higher rate of major bleeding events. The overall rate of deep venous thrombosis was 12.5% (forty-five of 361) in the fondaparinux group compared with 27.8% (101 of 363) in the enoxaparin group ($p < 0.001$). There was no difference in the rate of proximal deep venous thrombosis between the fondaparinux and enoxaparin groups (2.5% [nine of 368] and 5.4% [twenty of 372], respectively). There were eleven major bleeding episodes in the fondaparinux group, and there was one major bleeding episode in the enoxaparin group.

Aspirin

Aspirin prophylaxis has been studied in four small single-center studies¹⁰²⁻¹⁰⁵, and it was compared with mechanical devices in three of them¹⁰²⁻¹⁰⁴. In those studies, a mechanical device alone provided effective prophylaxis, and no additional benefit was obtained with aspirin prophylaxis. Aspirin does reduce the overall rate of deep venous thrombosis after total knee arthroplasty, but it is not as effective as low-molecular-weight heparin, warfarin, or mechanical devices⁹.

Mechanical Prophylaxis

The efficacy of pneumatic compression boots has been demonstrated in four small single-center randomized trials^{88,102,104,106}. The overall rates of deep venous thrombosis in these studies ranged between 20% and 38%, and the rate of proximal deep venous thrombosis was only 7%. The overall risk reduction in the four studies was 56%, but a total of only 110 patients were treated with pneumatic compression boots in these four studies⁹.

The efficacy of intermittent plantar compression after total knee arthroplasty has also been analyzed in four small studies^{72,73,95,103}. The overall risk reduction in these studies was 37%, but the combined enrollment was only 172 patients⁹. The largest of the four studies, which included 122 patients (164 knees), demonstrated a significant reduction ($p < 0.001$) in the overall rate of deep venous thrombosis in patients treated with intermittent plantar compression and aspirin (twenty-two of eighty-one knees; 27%) compared with those treated with aspirin alone (forty-nine of eighty-three knees; 59%)¹⁰³. In two of the studies, a low-molecular-weight heparin was more effective than intermittent plantar compression in reducing the overall rate of deep venous thrombosis^{72,73}.

On the basis of these reports, both pneumatic compression boots and intermittent plantar compression appear to reduce thrombus formation after total knee arthroplasty. However, larger multicenter randomized trials comparing these mechanical devices with chemoprophylactic agents are necessary to critically evaluate their efficacy. These devices also need to be assessed in groups of patients with short inpatient hospital stays. Finally, surgeons are using these devices as adjunctive agents, especially since warfarin has a delayed onset of action and the low-molecular-weight heparins are not administered until the morning after the operative procedure. Studies need to be performed to determine if the use of these devices in such a setting provides additional protection for the patient.

Influence of Anesthesia on the Rate of Thrombosis

It is well documented in the literature that, when patients are not treated with any prophylaxis after total hip arthroplasty, those who have received spinal or epidural anesthesia have a decreased rate of thrombosis compared with those who have received general anesthesia^{23,74,107-109}. It has been hypothesized that the decrease in the formation of thrombi associated with regional anesthesia is due to the sympathetic blockade, with subsequent vasodilation and an increased blood flow to the lower extremities¹⁶. Total hip arthroplasty generally results in a hypercoagulable state secondary to systemic activation of the coagulation cascade (Fig. 2). Blood loss has been reported to be decreased with the use of epidural anesthesia alone or in combination with general anesthesia as compared with general anesthesia alone¹¹⁰. It has been hypothesized that, if loss of blood and transfusion requirements could be minimized, the formation of clots might be decreased^{23,107,111-113}. Over the past fifteen years, Sharrock et al.^{23,81,112-114} have assessed both deep venous thrombosis rates and coagulation parameters in patients who received hypotensive epidural anesthesia during total hip or knee arthroplasty. Multiple studies demonstrated extremely low rates of asymptomatic clots and symptomatic pulmonary emboli^{23,107,114}. Blood loss and transfusion requirements in these patients were also remarkably low compared with those in other studies. However, hypotensive epidural anesthesia requires considerable expertise, resources, and invasive hemodynamic monitoring. To our knowledge, hypotensive epidural anesthesia has not been compared with general or spinal anesthesia in a randomized trial to determine its true impact on rates of deep venous thrombosis.

Regional anesthesia has become quite popular over the past decade because pain relief can be obtained for a more prolonged period of time, particularly with epidural anesthesia, and because the patient's mental status is not impaired. However, to our knowledge, no randomized trial has been performed to compare deep venous thrombosis rates between patients who received regional anesthesia and those who received general anesthesia during total joint arthroplasty and for whom effective prophylaxis was used.

Spinal hematomas have been noted following the use of epidural anesthesia and low-molecular-weight heparins as prophylactic agents¹¹⁵. It must be recognized that pharmacologic agents that have a short half-life may increase the risk of bleeding complications when regional anesthesia is used. Epidural hematomas can occur when low-molecular-weight heparins are employed in combination with regional anesthesia, but these agents can be used safely as long as certain precautions are taken. The American Society of Anesthesiologists made the following recommendations regarding the use of low-molecular-weight heparins and epidural anesthesia¹¹⁶.

1. If blood is noted during either needle or catheter placement, the initiation of low-molecular-weight heparin prophylaxis should be delayed for twenty-four hours after the operative procedure.

2. A twice-daily regimen of low-molecular-weight hep-

arin started postoperatively may increase the risk of hematoma formation. The first dose of the heparin should be delayed for twenty-four hours postoperatively, and hemostasis must be ensured. If a continuous epidural technique is employed on the first night after the procedure, the catheter should be removed the next day and the first dose of low-molecular-weight heparin should be delayed for two hours after catheter removal.

3. Patients treated with a single daily dose of low-molecular-weight heparin can receive the first dose (usually a half-dose) six to eight hours after the operation. The second dose should be given no sooner than twenty-four hours after the first dose. Indwelling catheters can be maintained, but the catheter should be removed ten to twelve hours after the last dose of low-molecular-weight heparin. The heparin should not be given for a minimum of two hours after catheter removal.

4. When an oral anticoagulant such as warfarin is used, the epidural catheter should be removed when the international normalized ratio is <1.5 . If warfarin is given the night before the operation, the international normalized ratio should be checked before the epidural catheter is inserted¹¹⁶.

Duration of Thromboprophylaxis

The optimal duration of thromboprophylaxis following elective total hip or knee arthroplasty remains controversial. There is a perceived risk of increased bleeding episodes as well as wound complications in patients who are treated with prolonged oral or subcutaneous anticoagulant therapy. Although the initial stimulus for thrombus formation occurs during the perioperative period, clinically detectable clots most likely develop later in the postoperative course²⁶.

As previously stated, White et al.²⁶ noted that the median time to diagnosis of symptomatic deep venous thrombosis after total hip arthroplasty was seventeen days and 76% of the symptomatic clots occurred after hospital discharge. In contrast, after total knee arthroplasty, the median time to diagnosis of symptomatic deep venous thrombosis was seven days and approximately half (42%) of the patients were diagnosed after hospital discharge. These findings suggest that there are differences in the temporal patterns of the formation of symptomatic deep venous thrombosis after total hip and knee arthroplasties and that perhaps different durations of prophylaxis may be appropriate²⁶.

In eight randomized trials of prolonged prophylaxis (twenty-eight to thirty-five days) after total hip arthroplasty, a low-molecular-weight heparin was compared with a placebo^{38,90-92,97,117-121}. In each study, patients received a low-molecular-weight heparin while they were in the hospital but then were randomized to receive a low-molecular-weight heparin or a placebo after discharge. Patients who received prolonged post-discharge prophylaxis had a substantial reduction in the rate of venography-documented asymptomatic deep venous thrombosis (9.6% compared with 19.6% in the placebo group)^{38,90-92,97,117-122}. Eikelboom et al. performed a meta-analysis of randomized trials to determine the effect of

prolonged prophylaxis on rates of deep venous thrombosis following total hip or knee arthroplasty¹²². Nine studies (3999 patients) met the eligibility criteria; eight of them evaluated a low-molecular-weight heparin and one, an unfractionated heparin. When compared with a placebo, prophylaxis for an extended duration (thirty to forty-two days) was associated with a significant risk reduction (1.4% compared with 4.3%, odds ratio = 0.33, 95% confidence interval = 0.19 to 0.56) in symptomatic deep venous thrombosis. The knee-replacement studies showed a smaller reduction in the rate of symptomatic deep venous thrombosis (1.0% compared with 1.4%, odds ratio = 0.74, 95% confidence interval = 0.26 to 2.15) that was not significant. There was no difference in the rate of major bleeding episodes between the extended-duration prophylaxis and the placebo group, but there was a significant increase in the rate of minor bleeding episodes (3.7% compared with 2.5%). The authors did not differentiate between bleeding in patients with total hip replacement and bleeding in those with total knee replacement. A major limitation of this meta-analysis was the unavailability of trials assessing the efficacy of extended duration prophylaxis with oral anticoagulants.

Heit et al.⁹⁷ performed a randomized, double-blind, placebo-controlled study to evaluate the effectiveness of extended-duration low-molecular-weight heparin therapy following total hip or knee replacement. The authors randomized 1195 patients to receive either short-term therapy (four to ten days) or extended-duration therapy (six weeks) with ardeparin. Following hospital discharge, there was no difference in the rates of duplex-ultrasound-documented deep-vein thrombosis (1.5% in the extended-treatment group and 2.0% in the placebo group; $p > 0.2$) or in the rates of major or minor bleeding episodes (two cases in the extended-treatment group and three in the placebo group; $p > 0.2$). The authors concluded that extended-duration prophylaxis with ardeparin did not significantly reduce the cumulative incidence of symptomatic venous thromboembolism or death after total hip or knee arthroplasty. A weakness of the study was that data on the hips and knees were evaluated together rather than separately.

There are data supporting the use of extended-duration prophylaxis after total hip arthroplasty¹²³. However, a major problem in determining whether prophylaxis should be prolonged for twenty-eight to thirty-five days is that symptomatic venous thrombosis or pulmonary embolism was not assessed as an end point in most of the studies. In addition, the studies usually compared in-hospital prophylaxis (five days) with prolonged prophylaxis (twenty-eight to thirty-eight days). It would be more relevant to compare prophylaxis lasting for twenty-eight or thirty-five days with two weeks of prophylaxis rather than with prophylaxis stopped at the time of discharge. This is particularly true when evaluating warfarin prophylaxis^{123,124}. There is general agreement that warfarin prophylaxis should be continued beyond hospital discharge¹²⁴. In the majority of patients, the target international normalized ratio is not achieved until the third postoperative day, which is often the time when they are discharged from the hospital. How-

ever, there are still concerns related to adverse effects of, and patient compliance with, out-of-hospital monitoring. The results of randomized trials and cohort studies indicate that approximately ten to fourteen days of prophylaxis should be adequate for most patients^{38,41,48,49,67,85,100,123,125,126}. Another regimen that has been proposed is aspirin prophylaxis for one month after ten days of warfarin, low-molecular-weight heparin, or fondaparinux therapy^{123,127}. Clearly, additional studies assessing rates of symptomatic deep venous thrombosis are necessary to determine the optimal duration of prophylaxis. It seems that the ultimate goal should be to stratify patients on the basis of the risk of the development of symptomatic venous thromboembolic disease. More prolonged prophylaxis should be considered following total joint arthroplasties in patients who are at higher risk, including those with a history of venous thromboembolic disease, limited mobilization, obesity, and cancer^{123,127}. In the future, genetic testing may help clinicians to identify patients who need prolonged chemoprophylaxis.

Screening Considerations

There has been a continuing trend toward a decrease in the length of the hospital stay following primary total hip and knee arthroplasties^{128,129}. Because of concerns about compliance and bleeding as well as difficulties with outpatient monitoring, some surgeons have been reluctant to continue postoperative prophylaxis following discharge from the hospital. Postoperative screening protocols have been developed because even the most effective forms of prophylaxis are associated with venous thromboembolic events and pulmonary emboli following discharge^{10,130}. However, despite the improvement in imaging modalities, screening studies appear to be the most effective for detection of symptomatic venous thromboemboli^{131,132}. Venous ultrasonography is clearly the most popular screening tool used today. It is a painless noninvasive diagnostic imaging technique that provides a two-dimensional cross-sectional representation of tissue and direct visualization of the thrombus. Venous ultrasonography can reliably detect thrombi in the proximal veins of symptomatic patients, but its efficacy as a screening tool remains controversial because of concerns related to its ability to accurately detect proximal thrombi in asymptomatic patients^{67,133-138}. Other potential problems with using ultrasound as a screening tool are its dependence on the skill of the operator and the logistics of obtaining scans prior to discharge with reduced inpatient hospital stays^{131,139}.

The issue of interobserver variability becomes more critical when patients are to be discharged over a weekend. In general, it appears to be safer and more cost-effective to continue prophylaxis after discharge than to develop and maintain a screening program^{67,123}.

Recommendations (Table III)

Total hip and knee arthroplasties are successful procedures that eliminate pain and enhance function. However, patients treated with these procedures are at high risk for venous thromboembolic disease and pulmonary embolism, and there is general agreement that they require prophylaxis against deep venous thrombosis^{9,16,123}. An ideal prophylactic regimen has not been identified, and the selection of an appropriate agent is usually a balance between efficacy and the risk of bleeding. The most effective prophylactic agents for these patients include low-molecular-weight heparin, warfarin, and fondaparinux. Aspirin reduces the risk of deep venous thrombosis compared with that associated with a placebo, but it does not appear to be as effective as warfarin or the low-molecular-weight heparins¹²³. Mechanical devices appear to provide effective prophylaxis after total knee arthroplasty, but they have not been studied as extensively as the chemoprophylactic regimens, and new studies are necessary to evaluate their efficacy in light of the reduction of hospital stays. The selection of a prophylactic regimen is influenced by the experience of the surgeon and individual patient factors. The ideal duration of prophylaxis after total joint arthroplasty has not been established, but a minimum of ten to fourteen days is safe and effective¹²³. There are data suggesting that a prolonged duration may increase the efficacy of prophylaxis following total hip arthroplasty, but further study is necessary. However, more prolonged prophylaxis should be considered for patients with a history of venous thromboembolic disease or other risk factors. Routine screening has not been shown to be cost-effective¹³¹. The goal in the future is to stratify patients according to risk as determined with genetic screening to select the most appropriate agent and duration of prophylaxis.

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