



PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLIC DISEASE IN PATIENTS HAVING A TOTAL HIP OR KNEE ARTHROPLASTY

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Patients undergoing total joint replacement are particularly prone to thromboembolic complications with potentially life-threatening consequences^{1,3}. Charnley et al., in a series of 7959 total hip replacements performed between 1962 and 1973, reported that the prevalence of nonfatal pulmonary embolism was 7.89% and that the prevalence of fatal pulmonary embolism was 1.04%^{4,5}. Similarly, in 1974, Coventry et al.⁶ identified an overall prevalence of pulmonary embolism of 2.2% in a series of 2012 consecutive total hip replacements; in a subset of patients who had received no prophylactic anticoagulation, the prevalence of fatal pulmonary embolism was 3.4%. However, the average duration of the operation was 2.4 hours, the average total blood loss was 1650 mL, and the average amount of blood transfused was 1144 mL. Prophylactic anticoagulation with warfarin was started five days after the operation. On the average, patients were managed with bed rest for one

week prior to walking and were discharged three weeks after the operation⁶. The prevalence of deep venous thrombosis after total knee arthroplasty is greater than that after total hip arthroplasty. Deep-vein thrombosis is far more refractory to available means of prophylaxis but since the prevalence is greater in the distal part of the limb, symptomatic and fatal pulmonary emboli are far less common. Moreover, it is essential to recognize that thromboembolic disease is manifested clinically as two very different conditions after hip and knee arthroplasty^{7,8}.

Prior to the acceptance of routine prophylaxis, proximal (femoral and popliteal) deep venous thrombosis accounted for 50% to 60% of all observed deep-vein thrombi after total hip arthroplasty. Currently, with warfarin prophylaxis, 90% of deep-vein thrombi occur in the calf and $\leq 10\%$ are found in the thigh. In addition, nearly all proximal thrombi are segmental in nature, frequently occur in the region of the

femoral vein near the lesser trochanter, and do not communicate with more distal thrombi in the calf. The situation after total knee replacement is considerably different. Without prophylactic anticoagulation, approximately 90% of all deep-vein thrombosis after knee replacement occurs in the calf veins, with proximal thrombosis occurring infrequently and accounting for $< 10\%$ of all thrombi. Proximal thrombosis after total knee arthroplasty is nearly always contiguous with more distal disease in the calf and rarely extends more proximally than the popliteal vein. Unlike that after total hip arthroplasty, the regional distribution of deep venous thrombosis after knee replacement has remained unchanged under the influence of warfarin prophylaxis. In addition, the prevalence of deep venous thrombosis after knee replacement with warfarin prophylaxis remains between 35% and 55%. While admittedly an improvement from the 80% to 90% rates that have been observed after total knee

replacement prior to routine prophylaxis, this residual rate remains far more refractory to prophylactic warfarin anticoagulation than that observed after hip replacement. In the setting of both hip and knee replacement, a systemic diathesis for clotting is activated, as bilateral venograms have revealed a 10% to 15% prevalence of deep-vein thrombosis in the uninvolved limb following each procedure⁹. It is unclear whether the use of a tourniquet during total knee replacement aggravates the propensity for clotting by causing venous stasis in the leg or whether the stimulation of endothelial cell-mediated fibrinolysis mitigates this effect and actually results in a lower prevalence of thrombosis than might occur without use of a tourniquet.

Finally, two caveats concerning the knee deserve special mention. The envelope of skin surrounding the knee is much less forgiving than that around the hip, and, therefore, a wound hematoma is less well tolerated after knee replacement than it is after hip replacement. Also, thrombosis in the calf is generally less feared than proximal deep venous thrombosis because of the lower risk of direct embolization. Nonetheless, in the postoperative period, 17% to 25% of clots in the calf propagate to the thigh and thereafter carry a greater risk of embolization¹⁰. There is a risk of undertreating these clots in the calf if guidelines for their management are derived from the literature involving medical patients.

During the past decade, substantial advances have been made in the understanding of the pathophysiology and prevention of venous thromboembolism, particularly that associated with total hip replacement¹¹⁻¹⁵. Warwick et al. reported that the prevalence of fatal pulmonary embolism in the absence of prophylactic anticoagulation was 0.5% following 1162 total hip replacements performed with contemporary operative techniques in the United Kingdom¹⁶. In North America, warfarin prophylaxis and the collective use of predeposited autologous blood, expeditious operative treatment, and early mobilization appear to have lowered

the rate of fatal pulmonary embolism even further, to <0.1% in several studies¹⁷⁻¹⁹. An increased awareness of the intense activation of the clotting cascade that occurs intraoperatively and persists for more than twenty-four hours postoperatively has recently underscored the importance of intraoperative events^{13,20,21}. Specifically, it has been established that activation of the clotting cascade occurs during instrumentation of the medullary canal in the setting of hip arthroplasty²², and one might logically expect a similar phenomenon during intramedullary instrumentation of the distal part of the femur in the setting of knee replacement. The problem is compounded by stasis in the lower extremity due to obstruction of femoral venous flow²³⁻²⁵, either while the lower extremity is kept in an extreme position to provide adequate exposure for preparation of the femur and insertion of a femoral component during hip replacement, or as a result of tourniquet use during knee replacement. Moreover, this kinking of the femoral vein can produce endothelial injury, providing the nidus for the formation and propagation of clots.

Warfarin Prophylaxis

Over the past three decades of experience with total hip and knee replacement in North America, the focus on thromboembolic disease has sharpened considerably. In 1986, the National Institutes of Health Consensus Development Conference Statement endorsed the routine use of anticoagulants as prophylaxis against thromboembolic disease after elective total joint replacement and treatment of hip fracture²⁶. An understandable preoccupation with bleeding complications was subsequently responsible for the slow acceptance of anticoagulation prophylaxis, but Paiement et al. reported that the increasing use of pharmacologic methods has had a favorable impact on mortality rates related to thromboembolism^{27,28}. Coventry et al.²⁹, in their landmark study of 2012 total hip arthroplasties, reported that the prevalence of fatal pulmonary embolism was reduced from 3.4% in patients who did not

receive anticoagulation to 0.05% in patients who received warfarin prophylaxis. Notably, they delayed the start of anticoagulation prophylaxis until the fifth postoperative day, presumably because of concern about bleeding problems in the early postoperative period, but still observed a 4.1% rate of bleeding complications in patients receiving warfarin. In a similar report on clinically evident pulmonary embolism following total hip replacement, Amstutz et al. administered warfarin for three weeks postoperatively, even when this period extended beyond the date of hospital discharge¹⁷. A symptomatic nonfatal pulmonary embolism that was confirmed with ventilation-perfusion scanning or angiography was noted after fourteen (0.5%) of 3000 total hip replacements. In a follow-up survey conducted by mail, those authors identified five additional nonfatal symptomatic pulmonary emboli (prevalence, 0.17%) that had occurred following hospital discharge in patients who had received warfarin prophylaxis for an average of 11.6 days. In a recent series of 1638 patients undergoing total joint replacement with use of routine warfarin prophylaxis, Pellegrini et al. noted an overall six-month mortality rate of 0.79%, with two fatal pulmonary emboli (prevalence, 0.12%) accounting for only 15% of deaths from all causes⁹.

Notwithstanding the apparent reduction in the prevalence of fatal thromboembolic disease with the more widespread use of routine anticoagulation prophylaxis, venous thromboembolism remains the most common reason for emergency readmission following total joint replacement³⁰. Indeed, in the above-mentioned series of 1638 patients undergoing total joint arthroplasty who were managed with routine venographic surveillance and warfarin prophylaxis, the overall six-month readmission rate was 1.3% (twenty-two of 1638). Of greater interest, the rate of readmission for venous thromboembolic events after total hip arthroplasty (1.8%; nineteen of 1079) was more than three times greater than that after total knee replacement (0.54%; three of 559) ($p = 0.04$)⁹.

Despite this decrease in both morbidity and mortality with warfarin prophylaxis, the reported rate of venographically evident deep-vein thrombosis after total hip replacement has ranged from 9% to 26% and the prevalence of proximal thrombosis has ranged from 2% to 5%^{19,30,34}. In comparison, the overall prevalence of deep-vein thrombosis after knee replacement performed with warfarin prophylaxis has ranged from 35% to 55% and the prevalence of proximal thrombosis has ranged from 2% to 14%^{19,33,34}.

Warfarin has been shown to be more effective for prophylaxis against proximal deep venous thrombosis than against distal thrombosis after total hip replacement, as illustrated in several trials comparing warfarin with pneumatic compression devices³⁵⁻³⁷. In at least three series^{33,38,39} specifically concerned with total hip replacement, the overall rate of deep venous thrombosis was not significantly different between patients managed with pneumatic compression and those managed with warfarin. Interestingly, in these studies there was a complementary decrease in the prevalence of distal thrombosis and a worrisome increase in the prevalence of proximal deep venous thrombosis with use of pneumatic compression, suggesting the relative ineffectiveness of thigh-high pneumatic compression sleeves when directly compared with warfarin for prophylaxis against proximal thrombosis^{33,38,39}. Paiement et al.^{39,40} compared the effect of intermittent pneumatic compression (sixty-six patients) with that of warfarin (seventy-two patients) after total hip replacement. The overall prevalence of deep venous thrombosis in the two groups was not statistically different, but the location of the thrombi (as determined with use of radiographic phlebography) was different. Specifically, intermittent pneumatic compression offered better protection against thrombi in the calf and warfarin offered better protection against thrombi in the thigh. Similar results were reported by Francis et al.³³ in a series of 201 patients managed with total hip replacement. In that study, the overall prevalence of deep venous thrombo-

sis (as determined with use of screening contrast venography) was 31% in patients treated with warfarin and 27% in those treated with pneumatic compression. Intermittent pneumatic compression provided a significant reduction in the prevalence of distal deep venous thrombosis (12% compared with 21%; $p = 0.021$), whereas warfarin resulted in a significant decrease in the prevalence of proximal deep venous thrombosis (3% compared with 12%; $p = 0.012$). In that study, proximal thrombi were typically located within 15 cm of the femoral head and were segmental and not continuous with thrombi in the deep veins of the calf.

Recent evidence has suggested that a combination of continuous epidural anesthesia and postoperative epidural analgesia along with warfarin is more effective for the prevention of deep venous thrombosis than either modality used alone³². In a study of 322 consecutive patients undergoing unilateral total hip replacement, warfarin was used to prolong the international normalized ratio to between 2.0 and 2.5^{13,32}. An epidural catheter was placed preoperatively and was maintained for thirty-six to forty-eight hours postoperatively for pain management with an infusion of bupivacaine and fentanyl. With an average hospital stay of 4.7 days, 259 patients completed contrast venography prior to discharge. The overall prevalence of venographic deep venous thrombosis was 8.9% (twenty-three of 259), with seventeen distal thrombi (6.6%) and six proximal thrombi (2.3%). Counter to historical experience, all of the proximal thrombi were contiguous popliteal extensions of thrombi in the calf and there were no segmental thrombi in the femoral vein. None of the twenty-three patients who had been managed with twelve weeks of warfarin therapy because of venographic evidence of deep venous thrombosis had further thromboembolic disease-related events or bleeding. The 236 patients who had normal venographic findings were all discharged without further anticoagulation prophylaxis. Two (0.8%) of these 236 patients were readmitted for symptomatic

thromboembolic disease; specifically, one deep venous thrombosis occurred in the thigh of a patient with a bilateral Syme amputation and one nonfatal pulmonary embolism occurred in another patient who was admitted to a different hospital. There were no wound hematomas requiring reoperation and no other morbid bleeding events. These data confirmed the previously reported findings of Westrich and colleagues, who observed an overall prevalence of venographic deep venous thrombosis of 10.3% in a study of 2037 patients who had undergone total hip replacement and had received hypotensive epidural anesthesia in conjunction with aspirin as prophylaxis against thromboembolic disease⁴¹. The rate of proximal deep venous thrombosis was 4.3%, and the rate of late symptomatic pulmonary embolism in patients with negative venographic findings was 0.44% (eight of 1826).

The prevalence of deep venous thrombosis and the risk of bleeding complications in patients managed with a combination of warfarin and epidural anesthesia compare favorably with the results associated with the use of any pharmacologic regimen alone, including fractionated heparins. Both extended epidural analgesia, which is contraindicated with use of fractionated heparins⁴², and early mobilization are likely to contribute to the low prevalence of deep venous thrombosis and to improve upon the 20% rate associated with warfarin alone. Most provocative is the observation that segmental proximal thrombosis, which accounts for as much as 50% of all deep venous thrombosis after total hip replacement, did not occur with this regimen of combined prophylaxis^{13,32}, perhaps because of the enhanced endothelial fibrinolysis that is known to occur with use of epidural anesthesia. The use of warfarin in conjunction with continuous epidural anesthesia or analgesia and early patient mobilization after total hip replacement is an effective strategy for prophylaxis against thromboembolic disease and does not carry the risk of bleeding complications that has been associated with newer fractionated heparins.

Bleeding Complications

Bleeding complications that occur after arthroplasty in patients treated with warfarin prophylaxis have been a source of concern. Occasionally, these complications were severe enough to result in death⁴⁵. More recent recommendations favoring reduced-intensity anticoagulation with a target prothrombin-time ratio of 1.3 to 1.5 times control, or an international normalized ratio of 2.0 to 2.5, have been associated with lower rates of bleeding complications⁴⁴⁻⁴⁶. Amstutz et al.¹⁷ noted an overall rate of bleeding complications of 1.5% (forty-four of 3000) after total hip replacement. The rate decreased from 4.7% to 1% after the target prothrombin time was reduced from a range of eighteen to twenty seconds (prothrombin-time index, 1.5 to 2.0) to a range of sixteen to eighteen seconds (prothrombin-time index, 1.3 to 1.5) and a bedside flowsheet was implemented to monitor daily prothrombin times and warfarin dosing. Of the forty-four major bleeding complications that were reported, thirty-six were wound hematomas and eight involved gastrointestinal or genitourinary-tract bleeding; there were no related deaths.

Pellegrini et al., in a study of 1079 consecutive patients undergoing primary or revision total hip replacement, observed an overall rate of bleeding complications of 1.2% using a target prothrombin-time index of 1.3 to 1.5¹⁹. In contrast, Paiement et al. reported a rate of major in-hospital bleeding complications of 3.7% (ten of 268) after total hip replacement; the ten major complications included nine wound hematomas and one gastrointestinal hemorrhage²⁸. When minor bleeding episodes were included, the overall rate of in-hospital bleeding complications was 6%. An additional thirteen patients (5%) had a minor bleeding episode during twelve weeks of extended warfarin prophylaxis after discharge. In a similar study in which 125 patients were managed with a structured program of outpatient warfarin prophylaxis for four weeks after total hip replacement, Reis et al. reported a rate of bleeding complications of 3.2%; no patient required readmission for bleeding complications⁴⁷.

Non-wound-related bleeding complications in orthopaedic patients receiving anticoagulation therapy predominantly involve the gastrointestinal and genitourinary tracts^{19,28,47}. Orthopaedic studies involving a few hundred patients, by design, possess adequate statistical power to investigate thromboembolic disease with a venographic prevalence of 20%. However, the lower prevalence of bleeding complications, in the range of 1% to 5%, usually renders studies of this size unable to demonstrate significant associations between bleeding rates and various anticoagulation therapies.

The rate of bleeding complications associated with warfarin prophylaxis has received renewed scrutiny specifically in comparison with that observed in association with use of the newer fractionated heparins, which have demonstrated improved efficacy in reducing the prevalence of deep venous thrombosis^{12,30,31,34,48-52}. In a meta-analysis of methods employed for the prevention of deep venous thrombosis after hip replacement, Imperiale and Speroff reported that the risk of clinically important bleeding complications in patients receiving low-molecular-weight heparins was sixfold greater than that in controls and 50% greater than that in patients receiving warfarin⁵³. In what we believe to be the largest direct comparison in the literature, Hull et al. studied 795 patients who received either a low-molecular-weight heparin (logiparin) or warfarin after total hip replacement. The prevalence of deep venous thrombosis in the logiparin group (20.8%) was modestly (but not significantly) lower than that in the warfarin group (23.2%)³⁰. However, this was offset by an increase in bleeding complications. Major bleeding complications were observed in eleven (2.8%) of the 398 patients in the logiparin group, compared with six (1.5%) of the 397 patients in the warfarin group. The prevalence of wound hematoma in the logiparin group (5.8%; five of 398) was more than twice as high as that in the heparin group (2.5%; ten of 397) ($p = 0.03$). In a prospective, controlled study comparing the efficacy of dalteparin with that of

warfarin in 580 patients undergoing total hip replacement, Francis et al.³⁴ reported that the overall venographic prevalence of deep venous thrombosis was 15% in the dalteparin group and 26% in the warfarin group ($p = 0.006$) while the prevalence of proximal deep venous thrombosis in these two groups was 5% and 8%, respectively ($p = 0.18$). The overall rates of major bleeding events were not significantly different between the groups (2.2% in the dalteparin group compared with 1.4% in the warfarin group). Nonetheless, the rate of red-blood-cell transfusion in the dalteparin group was significantly higher than that in the warfarin group (48% compared with 31%; $p = 0.001$), and the rate of bleeding complications on the operative side was more than four times higher in the dalteparin group than in the warfarin group (4.4% compared with 1%; $p = 0.03$)³⁴. One patient in the dalteparin group had transient thrombocytopenia and required reoperation for evacuation of a draining hematoma. Most recently, investigators reporting on the North American Fragmin Trials noted that the rate of major wound-related bleeding complications in the preoperative Fragmin group (8.3%) was significantly higher than that in both the postoperative Fragmin group (6.1%) and the postoperative warfarin group (3.9%) ($p = 0.03$)¹².

Colwell et al. compared the rates of clinically evident venous thromboembolic disease after total hip replacement in two groups of patients who received either adjusted-dose warfarin (1494 patients) or enoxaparin at a dose of 30 mg/12 h (1517 patients)⁴⁸. All clinically suspected events were confirmed by objective testing. Pharmacologic prophylaxis was administered for an average of 6.5 days in each group, and venous thromboembolic events were monitored for three months following hospital discharge. The prevalence of confirmed venous thromboembolism was 3.6% in the enoxaparin group and 3.8% in the warfarin group at the time of final follow-up. Thromboembolic events that occurred during the period of hospitalization were more common in the war-

farin group (prevalence, 1.1% in the warfarin group compared with 0.3% in the enoxaparin group), whereas those that occurred following hospital discharge were more common in the enoxaparin group (prevalence, 2.7% in the warfarin group compared with 3.3% in the enoxaparin group). Clinically important bleeding occurred in twenty patients (1.3%) in the enoxaparin group and in eight patients (0.5%) in the warfarin group. Analysis of the bleeding events revealed that 78% of the patients in the enoxaparin group who had notable bleeding either had received the initial dose of enoxaparin within twelve hours after the operation or had received the drug twice a day rather than once a day. Similarly, Watson et al., in a case-control study of 152 patients who were managed with either enoxaparin or pneumatic compression for prophylaxis against venous thromboembolism, demonstrated an increase in bleeding events associated with the use of fractionated heparin⁵⁴. The postoperative drop in hematocrit was significantly greater in the enoxaparin group ($p = 0.003$), and major bleeding events occurred in 3.3% of the patients who had been treated with enoxaparin compared with 1.3% of those who had been treated with pneumatic compression. Similar to the observations of Colwell et al., patients who received the initial dose of enoxaparin more than ten hours postoperatively had significantly fewer complications than those who received the drug within ten hours after the operation ($p = 0.05$).

Low-Molecular-Weight Heparin

Low-molecular-weight heparins have been studied extensively and have been found to be safe and effective for prophylaxis against deep-vein thrombosis after total joint replacement. Currently, there are three low-molecular-weight heparins approved by the Food and Drug Administration for such use in patients undergoing either total hip arthroplasty or total knee arthroplasty. These include enoxaparin (Lovenox) for patients undergoing both hip and knee arthroplasty, ardeparin (Normiflo) for those undergoing knee arthro-

plasty, and dalteparin (Fragmin) for those undergoing hip arthroplasty. Pharmacologically, low-molecular-weight heparin is substantially different from unfractionated heparin in that it binds less to protein and endothelial cells, resulting in a more predictable dose-response profile, a dose-independent mechanism of clearance, and a longer plasma half-life. With highly predictable pharmacokinetic properties and high bioavailability, low-molecular-weight heparin is also associated with a lower prevalence of thrombocytopenia than is unfractionated heparin and has the ability to target factor Xa while affecting factor IIa to a lesser extent than does unfractionated heparin. Because of their favorable pharmacokinetic properties, low-molecular-weight heparins can be administered subcutaneously once or twice daily without the need to monitor drug levels or activity⁵⁵.

In a review of twenty studies involving low-molecular-weight heparin prophylaxis in 3016 patients undergoing total hip arthroplasty, the total prevalence of deep venous thrombosis was 15% (95% confidence interval, 14% to 16%) with a relative risk reduction of 71%⁵⁶. In a review of eight studies involving low-molecular-weight heparin prophylaxis in 1499 patients undergoing total knee arthroplasty, the total prevalence of deep venous thrombosis was 31% (95% confidence interval, 29% to 33%) with a relative risk reduction of 49%⁵⁶. These results clearly indicate that low-molecular-weight heparin is, indeed, one of the best choices for prophylaxis against deep venous thrombosis in the settings of both hip and knee arthroplasty.

There has been a question of whether to start low-molecular-weight heparin prophylaxis within twenty-four hours after surgery, as is the practice in the United States, or preoperatively, as is the practice in Europe. In a recent North American study comparing low-molecular-weight heparin (begun either preoperatively or postoperatively) with adjusted-dose warfarin in patients undergoing total hip arthroplasty, the total prevalence of deep venous thrombosis in the preoperative and postoper-

ative heparin groups (10.7% and 13.1%, respectively) was lower than that in the warfarin group (24%). The prevalence of proximal deep venous thrombosis was 0.3% in both of the low-molecular-weight-heparin groups, compared with 3.0% in the warfarin group. The prevalence of major bleeding complications in the preoperative heparin group (8.9%) was significantly greater than that in the warfarin group (4.5%) ($p = 0.013$); however, the prevalence of such complications in the postoperative heparin group (6.5%) was not significantly different from that in the warfarin group¹². Concern regarding the possibility of increased bleeding with use of low-molecular-weight heparin remains. One trial showed an increase in bleeding complications⁵⁷, and another demonstrated greater blood loss³⁰ in association with the use of low-molecular weight heparin. Another study showed no significant difference between low-molecular-weight heparin and warfarin with regard to intraoperative and postoperative blood loss, decrease in hematocrit, or prevalence of major bleeding complications but did show a significantly higher prevalence of bleeding complications involving the operative site ($p = 0.03$) and a significantly higher rate of postoperative transfusion ($p = 0.001$) in association with low-molecular-weight heparin³⁴. The published literature therefore shows a clear dose-response relationship between increasing doses of fractionated heparin and decreasing rates of deep venous thrombosis, with an associated trade-off in the form of increasing rates of hemorrhagic complications. This point was well illustrated in a series of 568 patients described by Spiro et al., who conducted a dose-response study comparing three different regimens of enoxaparin (10 mg/d, 40 mg/d, and 30 mg/12 h) for prophylaxis against deep venous thrombosis after hip replacement⁵². The progressive reduction in the rate of deep venous thrombosis in these three groups (25%, 14%, and 11%, respectively) was associated with a significant increase in the overall rate of hemorrhagic events (5%, 11%, and 13%, respectively) ($p < 0.05$). The

use of fractionated heparins at a dose that is sufficient to significantly reduce the prevalence of deep venous thrombosis is associated with a higher rate of bleeding complications (especially those that are related to the operative wound) than is observed in association with the use of low-dose warfarin regimens. The increased efficacy of low-molecular-weight heparin in preventing deep venous thrombosis has to be weighed against the risk of increased bleeding.

The optimal duration of prophylaxis after total joint arthroplasty has been the subject of debate in recent years and remains uncertain. Initially, when the hospital stay for joint replacement ranged from seven to ten days, the duration of prophylaxis was extended to the length of hospitalization. Currently, the duration of hospitalization is four days or less, which may not provide an adequate duration of prophylaxis. Studies have suggested that the risk of deep venous thrombosis may persist for as long as two months after total hip arthroplasty^{19,58-60}.

The need for extended prophylaxis beyond the hospital stay was examined in six double-blind, randomized trials in which venographic deep venous thrombosis was used as the efficacy outcome⁵⁸⁻⁶³. In these trials, six to fourteen days of in-hospital prophylaxis was compared with thirty to thirty-five days of out-of-hospital prophylaxis with use of low-molecular-weight heparin. All studies demonstrated a 12% to 13% rate of asymptomatic deep venous thrombosis after hospital discharge with a further reduction in the range of 4% for in-hospital to 19% for out-of-hospital prophylaxis with low-molecular-weight heparin. Extended prophylaxis reduced the rates of total and proximal venographic deep venous thrombosis by more than 50%.

The prevalence of symptomatic deep venous thrombosis, however, has been shown to be similar in patients receiving prophylaxis and in those receiving placebo. In a large cohort study in which low-molecular-weight heparin was administered for a mean of 9.5 days after total joint replacement, the ninety-

day prevalence of symptomatic thromboembolism and fatal pulmonary embolism was 4.3% and 0%, respectively, in the group of 1142 patients who had had a hip replacement and 3.9% and 0.2%, respectively, in the group of 842 patients who had had a knee replacement⁶⁴. In a large clinical trial in which low-molecular-weight heparin or warfarin was administered for a mean of 7.3 days after total hip arthroplasty, the cumulative prevalence of symptomatic deep venous thrombosis between the time of discharge and twelve weeks after discharge was 3.4% in the group of 1516 patients who received low-molecular-weight heparin and 2.6% in the group of 1495 patients who received warfarin⁶⁵. In another study, extended prophylaxis with low-molecular-weight heparin was compared with placebo treatment for six weeks after surgery⁶⁶. The prevalence of symptomatic deep venous thrombosis or pulmonary embolism during the twelve weeks after hospital discharge was 1.5% in the group of 607 patients who received low-molecular-weight heparin compared with 2.0% in the group of 588 patients who received the placebo. The possibility of a small reduction in the rate of symptomatic deep venous thrombosis with extended low-molecular-weight heparin prophylaxis indicates that most patients who have had arthroplasty receive limited benefit from the prolonged prophylaxis.

Nonpharmacologic Thromboembolic Prophylaxis

The venous system returns deoxygenated blood from the periphery and organ centers to the lungs and heart. Since it is a low-pressure system, the venous walls are thin and the vascular compliance is high, making the venous system the major reservoir of blood. There are two physiologic mechanisms by which the venous system overcomes the pressure gradient and vascular resistance. First, active movement of the lower extremity increases muscle-compartment pressure and thereby compresses veins, forcing the blood back to the heart⁶⁷. Valves throughout the venous system of the lower extremity ensure that blood

flow is directed only toward the central vena caval system. There is controversy regarding whether pressure changes in the muscular compartments of the calf (the calf muscle pump) alone are sufficient to overcome the venous pressure gradient when the patient is in the upright position^{68,69}. The second physiologic mechanism is the venous pump of the foot⁷⁰. The plantar venous plexus is composed of one to four veins that course diagonally from the lateral part of the forefoot to the medial part of the sole at the level of the ankle⁶⁹. The diameter of these veins is almost twice that of the posterior tibial vein. During weight-bearing, the veins are compressed in the deep layer of the plantar surface⁷¹ and the plantar arch is flattened⁷², stretching the veins and resulting in a decrease in their diameter. This process generates enough force to overcome the pressure in the deep venous system of the calf. The plantar venous pump does not rely on active muscle contraction but on the forces exerted on the foot during weight-bearing^{70,72}. The blood flow is directed via valves within the plantar veins⁶⁹ mainly toward the posterior tibial vein.

Gardner and Fox advocated the use of pneumatic compression devices to simulate the physiologic venous pumps in the lower extremity in patients not yet walking after surgery⁷⁰. Pneumatic compression devices produce flow turbulence in the valve pockets, the main site for the initiation of thrombosis. In addition to these mechanical effects, it has been demonstrated that pneumatic compression increases the release of endothelium-derived relaxing factor, which inhibits platelet aggregation⁷³. Also, intermittent compression stimulates fibrinolysis by releasing mediators such as urokinase and/or tissue-plasminogen activator from the venous endothelium^{74,75}.

While the efficiency of pneumatic compression devices is not influenced by peripheral arterial disease⁷⁶, the augmentation of venous blood flow is reduced in patients who have had venous damage from a previous thrombosis⁷⁷. In addition to the increase in venous blood flow, pneumatic compression

causes an increase in arterial blood flow⁷⁸⁻⁸⁰. Each pneumatic impulse decreases the peripheral vascular resistance and thereby increases the arterial blood flow for approximately twenty-five seconds. This phenomenon was initially attributed to an increase in the arteriovenous pressure gradient alone, but hyperemia is also mediated by the endothelium-derived relaxing factor⁸¹. Shear stresses, which occur due to the rapid increase in blood flow and the increase in blood pressure in the intramuscular venules, cause the secretion of endothelium-derived relaxing factor, which diffuses to adjacent arterioles, causing vasodilatation and hyperemia^{72,82}. The duration of hyperemia matches the half-life of endothelium-derived relaxing factor (about twenty seconds). The amount of vasodilatation and hyperemia is primarily related to the rate of inflation of the compression devices and not to the duration of peak pressure. This may be attributed to the fact that rapid inflation, rather than the overall pressure, increases the shear stress on the vascular endothelium^{83,84}.

Postoperative immobilization causes venous stasis, resulting in an increase in venous volume and pressure within the lower extremity. The elevated pressure drives fluid into the interstitial space, causing edema. Therefore, an additional benefit of intermittent pneumatic compression devices is the resolution of venous congestion, thereby reducing compartmental pressure and concomitant pain and swelling^{85,86}.

Pneumatic compression devices increase the peak velocity of venous flow as well as the total volume of blood that is returned from the extremity to the heart. The exact increase in flow velocity and venous volume that is necessary to prevent deep venous thrombosis remains unclear⁸⁷. Current devices differ with regard to the location of application (foot, calf, or thigh), the number of chambers necessary for sequential compression, the total pressure applied, and the frequency of compressions as well as inflation time and holding time.

Compression of the plantar venous plexus should play an important role in increasing the venous blood flow;

however, in nonwalking patients, pneumatic compression devices are used in the supine position, when there is a substantial reduction in venous pressure. With the legs at the height of the right atrium, the venous pressure in the legs is decreased to approximately 5 mm Hg in the supine position, compared with 60 mm Hg in the sitting position and 90 mm Hg in the standing position. With the patient in the supine position, compression of the calf might be superior to compression of the foot because the venous volume in the calf is almost three times that in the foot. In the clinical setting, because of this increased blood volume, calf compression devices have demonstrated substantially greater volume augmentation and increases in the peak velocity of venous flow than have foot compression devices. Multichamber systems offering sequential inflation from the foot to the calf and/or thigh offer the greatest volume augmentation^{76,87} and are more effective than systems producing simultaneous, continuous compression^{88,89}. Considering the discomfort of the patient and the relative difficulty in handling the device, the advantage of additional thigh compression is questionable. With combined foot and calf compression devices, a delay of 0.5 to one second is appropriate before compression of the calf. Asymmetric compression is more efficient than circumferentially symmetric compression⁸³.

The applied pressure generated by a pneumatic compression device must exceed the average venous pressure in the limb. Moreover, approximately half of the energy delivered by the pressure impulse is lost to the tissues surrounding the venous vessels and to the elastic properties of the cuff itself. Current devices used for postoperative prophylaxis against deep venous thrombosis in nonwalking patients generate pressures of 160 mm Hg in the foot, 50 mm Hg in the calf, and 30 mm Hg in the thigh⁸⁷. A short inflation time (0.5 to one second) promotes an increase in net volume and peak flow, whereas prolonged compression does not increase the flow velocity or the total volume of blood mobilized^{82,83,90}.

Since the capacity of the veins in

the calf is three times greater than that of the plantar venous plexus, and assuming a constant rate of arterial inflow, it may take three times longer to refill the veins and to restore the resting venous pressure. Taking this into account, modern devices have an inflation frequency of three times per minute for foot pumps and once per minute for calf pumps. However, in reality, compression of the calf further increases the arterial inflow because of elevation of the arteriovenous pressure gradient and an increase in shear stress-mediated vasodilatation. An increase in the frequency of calf pump inflation to three or four times per minute may further increase venous blood flow with the patient in the sitting position. There are no clinical data in the literature on the effect with the patient in the supine position. However, the SCD Response Compression System (The Kendall Company, Mansfield, Massachusetts), a device that detects individual alterations in venous volume and initiates the next compression cycle as soon as the veins are fully refilled, may provide a method of physiologically controlling the frequency of compression⁹¹.

On the basis of *in vivo* flow studies, it appears that a calf compression device (with or without sequential foot compression) with an asymmetric multichamber system that applies at least 50 mm Hg of sequential external pressure at a frequency of at least once per minute with an inflation time of less than one second is the ideal device for prophylaxis against deep venous thrombosis in patients undergoing elective orthopaedic surgery^{87,92}.

Postoperative intermittent compression devices do not address the problem of thrombus formation during the operative procedure although intraoperative and early postoperative venograms confirm that thrombogenesis is primarily an intraoperative event^{10,93}. Intraoperative interventions such as heparin administration as well as hypotensive epidural anesthesia are used to reduce the intraoperative development of thrombi. Intraoperative application of pneumatic compression devices can be associated with neu-

rovascular compression or compartment syndrome⁹⁴ and peroneal nerve compression. Therefore, care must be exercised when compression devices are applied intraoperatively⁹⁵.

During total hip replacement, the positioning of the extremity for the preparation and implantation of the femoral component causes obstruction of the venous outflow^{14,93}. Excessive flexion together with adduction and internal rotation (posterior approach) or external rotation (anterolateral approach) causes twisting of the femoral vein, resulting in a decrease in intraoperative venous blood flow¹⁴. In vitro studies have shown that obstruction of the venous flow for ten minutes in the presence of a thrombogenic stimulus is sufficient to initiate clot formation⁹⁶. Therefore, whenever possible, flexion and adduction should be relieved during the implantation of the femoral component. Patients undergoing total knee replacement have stagnation of venous blood flow because of tourniquet use. Before the incision, the leg is exsanguinated and a thigh tourniquet is inflated to decrease intraoperative blood loss. This may explain why the majority of deep venous thrombi in patients undergoing total knee arthroplasty are detected within twenty-four hours after surgery¹⁰. Maynard et al. evaluated fifty-nine patients (seventy-six knees) undergoing total knee replacement¹⁰. Each patient had a venogram on the day of surgery or on the first postoperative day and another venogram four to seven days after surgery. Eighty-six percent of all patients who had deep venous thrombosis had a positive venogram within twenty-four hours after surgery. Additional evidence that thrombosis is initiated during the operation is the increase of coagulation markers after the release of the tourniquet⁹⁷.

There is activation of thrombogenesis during total hip arthroplasty as well²². Although the osteotomy of the femoral neck and the implantation of the acetabular component result in little activation of thrombosis, the reaming of the femur and the implantation of the femoral component have been associated with an increase of fibrinopep-

tide A, prothrombin F1.2, thrombin-antithrombin complexes, and D-dimer²². This increase is greater in patients managed with cemented, rather than cementless, femoral components. A single intraoperative dose of unfractionated heparin (15 to 20 IU/kg of body weight) administered before the preparation and insertion of the femoral component reduced the levels of fibrinopeptide A and prothrombin F1.2²². While a number of studies have confirmed the substantial impact of intraoperative heparin administration on the rate of deep venous thrombosis in patients undergoing total hip replacement⁹⁸, the data on patients undergoing total knee arthroplasty are less encouraging. Infusion of a bolus of heparin prior to inflation of the tourniquet and continuous heparin infusion until deflation has not been proven to further reduce the risk of deep venous thrombosis during total knee replacement^{99,100}. Intraoperative administration of heparin has not been associated with increased intraoperative or postoperative bleeding^{101,102}.

Local epidural anesthesia has been associated with a lower rate of deep venous thrombosis than general anesthesia has¹⁰³. This was first explained by the increase in venous flow and its direct effect on thrombogenesis¹⁰³. However, recent studies have failed to prove this direct impact on coagulation¹⁰⁴. Other explanations for the association between epidural anesthesia and a reduced prevalence of deep venous thrombosis include the benefits of hypotensive anesthesia and reduced blood loss. Venous blood flow increases when epinephrine is used to stabilize the blood pressure during hypotensive epidural anesthesia¹⁰⁵. Hypotensive epidural anesthesia (with maintenance of a mean arterial pressure of 50 to 60 mm Hg) reduces intraoperative blood loss during total hip replacement^{106,107}. Intraoperative blood loss necessitating transfusion is associated with an increased rate of deep venous thrombosis¹⁰⁸.

Clinical Studies

The prevalence of deep venous thrombosis after total knee or total hip ar-

throplasty without prophylaxis is unacceptably high^{109,110}. Two recent meta-analyses demonstrated the effect of prophylactic intervention on the prevalence of deep venous thrombosis as well as on the rate of pulmonary embolism in patients undergoing total knee¹¹ and total hip arthroplasty¹².

In a review of twenty-three studies, involving 6001 patients, selected from 136 articles published between 1980 and 1997, Westrich et al. reported that the prevalence of deep venous thrombosis after total knee replacement was 53% in patients treated with aspirin, 45% in those treated with warfarin, 29% in those treated with low-molecular-weight heparin, and 17% in those treated with pneumatic compression¹¹. Both low-molecular-weight heparin and pneumatic compression were significantly more effective for the reduction of deep venous thrombosis than aspirin ($p < 0.0001$) or warfarin ($p < 0.0001$). The rate of pulmonary embolism in the aspirin group (12%; 222 of 1901) was significantly higher than that in the other groups ($p < 0.05$). The authors did not distinguish between the prevalence of proximal and distal deep-vein thrombi.

Freedman et al., in a review of fifty-two studies involving 10,929 patients undergoing total hip replacement, reported that the rate of deep venous thrombosis was 48% in the placebo group, 31% in the aspirin group, 23% in the warfarin group, 21% in the pneumatic compression group, and 18% in the low-molecular-weight heparin group¹². Pneumatic compression was associated with the lowest risk of distal deep venous thrombosis; this risk was significantly lower than that in the aspirin group ($p = 0.0001$) or the warfarin group ($p = 0.0007$). However, the risk of proximal deep venous thrombosis in the pneumatic compression group (13.3%) was significantly higher than that in the low-molecular-weight heparin group (7.7%) and the warfarin group (6.3%) ($p = 0.0059$ and $p = 0.0004$, respectively). Distal and small proximal thrombi are associated with a low risk of pulmonary emboli¹¹³. The higher prevalence of proximal deep venous thrombosis in the pneumatic

compression group raises concern. However, the prevalence of a symptomatic pulmonary embolism in the meta-analysis by Freedman et al. was <1% in the low-molecular-weight heparin, warfarin, and pneumatic compression device groups. The aspirin group and the low-dose heparin group demonstrated a significantly ($p < 0.0083$) higher rate of symptomatic pulmonary embolism (1.3%) than did the warfarin and low-molecular-weight heparin groups. There were no significant differences between the groups with regard to the rate of fatal pulmonary embolism.

DiGiovanni et al. reported that the combination of intraoperative prophylaxis (hypotensive epidural anesthesia and heparin) and postoperative prophylaxis (aspirin and pneumatic compression) reduced the prevalence of proximal deep venous thrombosis after total hip arthroplasty to 2% (four of 198)⁹⁸. The same positive effect of combining pneumatic compression with pharmacological anticoagulation therapy has been described for patients undergoing total knee replacement. In the study by Westrich and Sculco, the combination of aspirin with pneumatic plantar compression resulted in an overall rate of deep venous thrombosis of 27% but a rate of proximal deep venous thrombosis of 0%⁹⁶. Woolson et al. found similar results with a combination of low-dose warfarin and pneumatic compression after total knee replacement; in their study, the rate of proximal deep venous thrombosis was reduced to 5%¹¹⁴.

We are not aware of any published randomized studies comparing the efficacy of different compression devices. There are, therefore, scant data documenting the relative advantages of calf, foot, and combined compression devices¹¹⁵. Westrich et al. recognized a positive correlation between the duration of plantar compression and the reduction in the rate of deep venous thrombosis¹¹¹. Compliance with the use of pneumatic compression devices is a problem¹¹⁶. This could cause less consistent results in the general patient population in comparison with those in well-supervised study populations.

Clinical trials involving a combi-

nation of compression devices and postoperative aspirin prophylaxis have demonstrated rates of proximal and distal deep venous thrombosis that are similar to those associated with the use of low-molecular-weight heparin, but with fewer major bleeding complications^{111,112,117}. The combination of pneumatic compression devices and aspirin might therefore be at least as cost-effective as low-molecular-weight heparin.

Westrich et al. recently reported on 2307 patients who underwent a total hip replacement under hypotensive anesthesia at the Hospital for Special Surgery between 1990 and 1993¹⁰⁷. Postoperatively, pneumatic compression devices and aspirin were used for prophylaxis against deep venous thrombosis. The overall rate of deep venous thrombosis was 10%, and the rate of proximal deep venous thrombosis was 4%. One patient (0.04%) died of a pulmonary embolism. Between 1994 and 1999, a single dose of 1000 to 1500 IU of heparin was administered intraoperatively with use of the same postoperative protocol. The overall rate of deep venous thrombosis increased to 7%, and the rate of proximal deep venous thrombosis decreased to 2%⁹⁸.

Discussion

With the use of improved operative and anesthetic techniques that afford accelerated rehabilitation, the prevalence of fatal pulmonary embolism following total hip arthroplasty has declined in recent years independent of the use of routine anticoagulation prophylaxis. Additionally, the use of predeposited autologous blood is associated with a reduction in the overall prevalence of venous thromboembolic disease¹¹⁸. Nevertheless, during the extended postoperative period, venous thromboembolism remains the single greatest threat to the life of the patient who has undergone total hip arthroplasty, raising the issues of the appropriateness and the type of routine prophylaxis. Beyond these intraoperative measures, the issue of routine chemical prophylaxis against venous thromboembolism remains controversial and has been recently challenged by the British

orthopaedic community^{119,127}. The suggestion of Murray et al. that the effectiveness of thromboprophylaxis should be assessed on the basis of *overall* mortality rates is plausible^{124,125}, but the concept put forth by Dunsmuir et al. of a so-called accelerated mortality after total hip replacement with no absolute effect on overall mortality is less intuitive¹²⁸. While mortality rates attributable to pulmonary embolism historically have ranged from 2.2% to 3.4%, an opportunistic meta-analysis from the United Kingdom of more recent publications suggested that the rate of fatal pulmonary embolism *in the absence of chemical prophylaxis* is approximately 0.1%¹²⁵. Smaller prospective series in North America have shown a rate of fatal pulmonary embolism of <0.1% along with a substantial reduction in the *overall* mortality rate to <0.8% with use of warfarin prophylaxis^{17,18}. As the extended three-to-six-month follow-up that is necessary for determination of mortality rates is more reliably achieved in single-center trials, the accuracy of pooled data from multicenter studies is actually less than that of smaller, single-center studies. However, the performance of a prospective, single-center trial to assess pulmonary embolism-related death would require > 50,000 patients, making it a practical impossibility. Given the limitations of these comparative data from different institutions and on the basis of a threefold-to-fivefold reduction in the prevalence of fatal pulmonary embolism, the consensus in North America supports routine anticoagulation therapy as prophylaxis against venous thromboembolic disease in patients undergoing total hip and knee arthroplasty.

The choice of postoperative prophylaxis is controversial. Warfarin, low-molecular-weight heparins, and the use of pneumatic compression devices in combination with aspirin are all acceptable. Warfarin has been used for the longest period of time and is probably the most common method. Greater experience and carefully conducted clinical trials are needed to determine whether one method is superior to another.

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