Deep Vein Thrombosis and Total Hip Replacement Surgery

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ABSTRACT

This article reviews the epidemiology and pathophysiology of deep vein thrombosis as it pertains to patients undergoing total hip replacement surgery. For comparison, rates of deep vein thrombosis and pulmonary embolism observed in different surgical populations are presented. Current diagnostic methods as well as those mentioned in the literature are explained.

The different mechanisms of action of the primary prophylactic drugs are briefly reviewed. The benefits of prophylaxis with warfarin, unfractionated heparin and low molecular weight heparins are discussed. Dosage schedules for patients undergoing total hip replacement surgery are presented. Non-drug prophylaxis is mentioned. Opportunities for prophylaxis after discharge are presented, as the duration of the period of risk after surgery has not yet been defined.

The results of clinical trials with these agents are briefly reviewed. Published metaanalyses evaluating agents available in Canada and related compounds are assessed. Although prophylaxis can greatly reduce the risk of thromboembolic events in this patient population, no agent can eliminate this risk. No specific prophylactic agent has provided consistently superior efficacy in reducing the risk of deep vein thrombosis in patients undergoing total hip replacement.

Key Words: deep vein thrombosis, heparin, low molecular weight heparins, total hip replacement surgery, warfarin.

RÉSUMÉ

Cet article examine l'épidémiologie et la physiopathologie de la thrombose veineuse profonde chez les patients ayant subi une arthroplastie totale de la hanche. Il compare les taux de thrombose veineuse profonde et d'embolie pulmonaire observés chez différents groupes d'opérés et explique les méthodes diagnostiques actuelles et celles mentionnées dans la littérature.

On y passe aussi en revue les différents mécanismes d'action des médicaments prophylactiques de première intention et on y discute des avantages des traitements prophylactiques à la warfarine, à l'héparine non fractionnée et à l'héparine de faible poids moléculaire. Des schémas posologiques pour les patients qui ont subi une arthroplastie totale de la hanche et des traitements prophylactiques non médicamenteux, sont présentés, ainsi que les options prophylactiques après la sortie du patient de l'hôpital, car on connaît encore mal la durée de la période de risque post-opératoire.

Cet article examine les résultats des essais cliniques avec les agents ci-dessus mentionnés, de façon brève, et les résultats de méta-analyses évaluant les médicaments et les agents connexes qui sont disponibles au Canada. Bien que le traitement prophylactique puisse réduire grandement le risque de thromboembolies chez cette population de patients, aucun médicament ne peut éliminer ce risque. Aucun agent prophylactique particulier n'a montré une efficacité supérieure aux autres de façon soutenue dans la réduction du risque de thrombose veineuse profonde chez les patients ayant subi une arthroplastie totale de la hanche.

Mots clés : arthroplastie totale de la hanche, héparine, héparine de faible poids moléculaire, prophylaxie, thrombose veineuse profonde, warfarine.

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INTRODUCTION

In 1989-90, Canadian hospitals performed 19,517 total hip replacement (THR) procedures.[1] Patients undergoing this surgery are at risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) during their post-surgical hospitalization and for a period of time after discharge. Additional factors have been identified that can further increase this risk. Appropriate prophylaxis can reduce, but not totally eliminate, the risk of these adverse outcomes.

By understanding the degree of risk as well as those factors that further increase the risk, pharmacists will be better able to recognize which surgical patients have the greatest need of prophylaxis. As well, the pharmacist will better understand the importance of patient compliance when prophylaxis is continued after the patient is discharged.

Epidemiology

In 1991, an American multi-centre study[2] determined the average annual incidence of initial DVT and PE to be 48 and 23 per 100,000, respectively, the observed rate of recurrent DVT was 36 per 100,000. In this study, patients diagnosed with an initial episode of DVT experienced an in-hospital mortality rate of 12%. Mortality was 30% in post-DVT patients followed for 3.5 years after hospital discharge, although comorbidities may have contributed. In both groups, mortality was strongly

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associated with increasing age. The incidence and case-fatality rates presented are not precise because of limitations associated with the clinical diagnosis of DVT and also a lack of autopsy data to confirm PE.[2]

Pathophysiology of Venous Thromboembolism and Pulmonary Embolism

In 1856, Virchow determined that stasis, vascular damage and hypercoagulability were the three principal factors that predisposed the patient to venous thrombosis (the presence of a thrombus within a vein and the vessel wall's subsequent inflammatory response).[3] Total hip replacement and other major lower limb surgery predisposes the patient to venous thrombosis in deep veins (as opposed to superficial veins).[3,4] The relationship between these factors and orthopedic surgery is illustrated in Table I.

Thrombus formation in the deep veins of the legs may occur during the prolonged period of general anesthesia required for lower limb surgery, as well as during the limited mobility phase afterwards.[5,6] Thrombus formation generally begins during the surgery and usually resolves without incident when the patient becomes mobile and the fibrinolytic system is restored, between the third and fifth post surgical days.[5,7,8] DVT may begin in the calf (distal DVT) or above the knee (proximal DVT). Clinical symptoms (calf discomfort, pain on forced dorsiflexion of the foot [Homan's sign]) may be absent in two-thirds of patients with DVT.[9,10] Thrombus formation occurs in the non operative leg in up to 25% of patients.[11-13] Many risk factors for DVT have been identified and are presented in Table II.

Table I. The Pathophysiologic Risk Factors in Orthopaedic Surgery [4]

Pathophysiologic Risk Factor	Surgical Causes of Increased Risk
stasis	venous return decreased by: supine position, surgical positioning of joint, anaesthesia (causes peripheral venous vasodilation)
vascular damage	surgical positioning of joint, excessive vasodilation from anaesthesia
hypercoagulability	changes associated with surgery include: decreased Antithrombin-III and tissue plasminogen activator, increased plasminogen activator inhibitor one

Table II. Risk Factors for Thromboembolism

Risk Factors
Surgery (orthopaedic, thoracic, abdominal, genitourinary; procedure > 30 minutes)
Neoplasms (pancreas, lung, ovary, testes, urinary tract, breast, stomach)
Trauma (fractures of spine, pelvis, femur, tibia)
Immobilization (post acute MI, CHF, CVA; postoperative convalescence, paralysis)
Increased age
Previous venous thromboembolism (DVT or PE)
Varicose veins
Pregnancy
Estrogen (high dose)
Cardiac dysfunction
Obesity
Venulitis (thromboangiitis obliterans)
Hypercoagulability states
inherited: deficiencies of antithrombin III, heparin cofactor II, protein C, protein S, tPA, plasminogen; dysfibrogenemia; dysplasminogenemia; defective tPA release; elevated levels of Plasminogen Activator Inhibitor-I anticardiolipid antibodies; hyperhomocysteinemia
acquired: lupus anticoagulants; myeloproliferative disorders (polycythemia vera, chronic myelogenous leukemia, essential thrombocythemia, myelofibrosis and myeloid metaplasia); Behçet's disease; ulcerative colitis; hypercholesterolemia; diabetes mellitus; heparin-associated thrombocytopenia and thrombosis

MI = myocardial infarction CVA = cerebrovascular accident
CHF = congestive heart failure DVT = deep vein thrombosis
PE = pulmonary embolism

A calf vein thrombus usually remains confined to the calf veins and frequently resolves spontaneously.[8] However, it may propagate and extend proximally into the veins above the knee. Such "proximal extension" may occur in up to 20% of cases.[8, 14] However, investigators are unable to reach a consensus concerning the precise rate of extension. For example, extension rates for distal DVT of 9% and zero percent have been reported.[6, 15] Many researchers believe that patients with DVT restricted to veins in the calf experience a very low risk of PE, but the degree of risk has not been quantified.[8, 13, 16-18] In addition, approximately 25% of THR patients develop proximal thrombi without calf involvement.[19]

There is a strong association between proximal DVT and PE.[1, 9, 20, 21] The risk of PE in patients with proximal DVT has been estimated to be about 50%, although patients may be asymptomatic and embolic damage may be subclinical.[8, 13, 14] Not surprisingly, proximal extension of distal DVT has been noted to increase the risk of PE.[8, 9, 16] In an early, prospective study of patients with clinically suspected PE employing ventilation-perfusion scanning, pulmonary angiography and venography, Hull et al observed that abnormal findings detected by perfusion lung scan correlated strongly to "extensive" DVT.[22] DVT and PE have been described as "two clinical presentations of the same disease."[23]

Patients over 40 years of age who are hospitalized for longer than five days and undergo a major surgical procedure are at increased risk of DVT and PE.[24] The incidence of DVT and PE is higher in patients undergoing orthopedic surgery compared with other types of surgery.[10] In patients undergoing THR and not receiving prophylaxis, the rates of DVT, PE and fatal PE have been reported as 50%, 15%, and 3%, respectively.[25] Rates for these events in different types of surgery are presented in Tables III and IV.

Table V illustrates the prevalence of DVT in patients undergoing surgery for THR or total knee replacement, based on reports from a small number of relatively recent trials. The incidence of proximal and distal DVT in these patients is also presented. The data presented in Tables III to V imply that these patient groups should each be considered unique and that their outcomes should not be aggregated.[10]

Table III. Mean Incidence of Postoperative Deep Vein Thrombosis in Surgical Patients Without Prophylaxis as reported by the respective authors.

Type of Surgery (Reference)	No. of Trials	No. of Patients	Mean Incidence of DVT
Total hip replacement[10]	13	655	51%
Hip fracture[24]	9	485	44%
Elective orthopaedic[7]	12	392	45%
Total knee replacement[10]	4	116	61%
Trauma[10]	6	689	53%
General[10]	54	4,310	25%

Table IV. Mean Incidence of Fatal Pulmonary Embolism in Surgical Patients Without Prophylaxis as reported by the respective authors.

Type of Surgery (Reference)	No. of Trials	No. of Patients	Mean Incidence
Elective hip surgery[24]	5	249	2.4%
Hip fracture[24]	13	1,040	5.9%
Traumatic orthopedic[24]	5	not stated	2.4%
General[10]	33	5,547	0.9%

Table V. Total, Proximal and Distal DVT Rates in THR and Total Knee Replacement Patients Without Prophylaxis

Procedure	No. of Patients	Incidence		
		Total DVT	Proximal DVT	Distal DVT
Total hip replacement				
Reference 5	54	35%	26%	9%
Reference 12	97	55%	29%	26%
Reference 19	39	51.3%	23.1%	28.2%
Reference 85	97	45%	36%	9%
Reference 86	51	45.1%	21.6%	23.5%
Range (of trials listed above)		35-55%	21.6-36%	9-28.2%
Total knee replacement				
Reference 10*	not stated	40%-84%	9%-20%	not stated
Reference 87	54	58%	19%	39%

* range presented represents authors' summary of four trials

Diagnosis of Deep Vein Thrombosis

As previously mentioned, clinical signs alone are too insensitive to be relied upon for the diagnosis of DVT.

Multiple differential diagnoses are possible for a patient presenting with calf discomfort and venous distension, and the diagnosis of DVT is confirmed in only 30% of patients with these symptoms.[26, 27] Dalen and Alpert reinforced the importance of establishing the correct diagnosis based on the association of PE with DVT. They determined that, based on autopsy studies, 11% of patients who subsequently develop PE die within the first hour.[28]

The gold standard for confirming the diagnosis of DVT is contrast venography, also known as ascending venography or phlebography.[29, 30] This is an invasive test that involves injecting radiopaque contrast medium into the distal dorsal foot vein to permit radiographic visualization of filling defects (usually indicative of thrombi) in the deep venous system. Venograms may be inadequate in between 4 to 12% of patients.[26] In addition, venography can be painful, and 1 to 2% of patients may develop a DVT due to the procedure itself.[26, 27] It also carries the risk of adverse reactions associated with the injection of iodinated radiocontrast media. For these reasons, venography is usually not repeated in the short term. However, venography remains the standard for comparison of newer diagnostic procedures.

^{125}I-labelled fibrinogen was once used to confirm the diagnosis in patients where DVT is suspected. This procedure is referred to as the fibrinogen uptake test (FUT). After injection, radiolabelled fibrinogen is incorporated into the thrombus as fibrin and scanning detects increased radioactivity at the site of the thrombus. Radiofibrinogen does not adequately detect thrombi in the upper thigh, partly because of the location of the surgical wound in hip replacement patients. Due to fear of blood-borne infection, ^{125}I-labelled fibrinogen has been withdrawn from the market.[26, 31, 32] It is mentioned here only because of frequent references to it in the literature.

Four diagnostic tests frequently reported in the DVT literature include impedance plethysmography, Doppler ultrasound, real-time B-mode ultrasonography and duplex scanning. The sensitivity and specificity of these tests in confirming the diagnosis of DVT in symptomatic patients approach those of venography. In applying these test methods in THR patients, the sensitivity and specificity may be lower than in other types of patients. However, these tests are non-invasive and are safer than invasive tests. In addition, serial testing allows the status of the patient to be monitored over time.[33]

Impedance plethysmography (IPG) involves rapid inflation and deflation of a pneumatic thigh cuff to change the blood volume distal to the cuff, resulting in changes in electrical resistance (impedance). The changes in resistance is measured by two calf electrodes.[26, 31, 32] IPG demonstrates high sensitivity and specificity for proximal DVT in symptomatic, non-orthopedic patients, but sensitivity in orthopedic patients and in asymptomatic patients is low.[26, 31] IPG has not gained widespread clinical usage due to difficulties in maintaining quality control.[23]

Doppler ultrasound (or Doppler flow velocity) uses an audible signal that assesses venous blood flow. This method is highly sensitive to occluded proximal veins, but is less sensitive to nonoclusive proximal thrombi and calf thrombi. The equipment is portable and easy to use, but performance of the test requires considerable skill and interpretation of the results is subjective.[26] Both sensitivity and specificity for proximal DVT in symptomatic patients are improved with the use of colour Doppler ultrasonography, although only a few trials have been reported. Colour Doppler screening of asymptomatic high-risk patients has demonstrated 48% sensitivity and 96% specificity for proximal DVT.[26]

Real-time B-mode ultrasonography uses high resolution real-time ultrasound to visualize veins and arteries in the tested limb. The presence of a thrombus will prevent the vein from collapsing under gentle compression from the ultrasound transducer, hence, the name "compression ultrasonography."[26, 31, 33] Fewer than 6% of patients have inconclusive test results.[25] B-mode ultrasonography demonstrates high sensitivity and specificity to detect proximal DVT in symptomatic patients, but has not been evaluated for the detection of calf vein thrombi.[26] As a screening tool for proximal DVT in asymptomatic orthopedic surgical patients, it has demonstrated 59% sensitivity and 98% specificity.[26]

Duplex scanning is a combination of real-time B-mode ultrasonography and Doppler or colour Doppler ultrasound.[33] Results are similar to those obtained with real-time ultrasound. It is possible that additional evaluation of Duplex scanning may improve the rate of detection of calf vein thrombosis.[26]

All testing is more successful in patients with their first DVT. Detection of recurrent DVT is more difficult due to changes in venous architecture. Screening of asymptomatic patients with recurrent DVT is also less effective.[26] Both invasive and noninvasive testing in symptomatic patients has been shown to be cost-effective, although venography is no longer recommended as a first-line test.[34,35] Depending on the availability of equipment, venography, Doppler ultrasound, or B-mode ultrasonography may be used in Canadian hospitals to confirm the diagnosis of DVT. A brief comparison of the sensitivities and specificities

of different tests in symptomatic patients is presented in Table VI.

Warfarin, Heparin and Low Molecular Weight Heparins — Mechanisms of Action

Although warfarin, unfractionated heparin and low molecular weight heparins have all been promoted for prophylactic use in patients undergoing THR and other surgical procedures, their mechanisms of action are different. Warfarin inhibits the production of vitamin K-dependent coagulation proteins (factors II, VII, IX and X).[36] Standard or unfractionated heparin (UH) molecules containing a unique pentasaccharide (about one-third of the total heparin molecules) which binds to antithrombin-III (AT-III) and this complex catalyses the rate of inactivation of coagulation enzymes factor IIa (thrombin), factor Xa and factor IXa.[37] The increased rate of inactivation of thrombin requires a large heparin molecule containing at least 18 saccharide units, equivalent to a molecular weight of at least 5,400 daltons, because both thrombin and AT-III must bind simultaneously to the heparin molecule.

Low molecular weight heparins (LMWHs) are fractionated heparin molecules containing a mean of 15 saccharide units; the molecular weights range between 4,000 and 6,500 daltons. Because fewer molecules contain the required pentasaccharide unit in comparison to UH, the ability to bind to AT-III and inactivate factor Xa is reduced as is the ability to inactivate thrombin.[37] Whereas UH has an anti-factor Xa to anti-factor IIa ratio of 1:1, the commercially available LMWHs have a ratio of between 4:1 and 2:1.

The development of LMWHs from UH and their use for thromboprophylaxis has been stimulated by their favourable pharmacological and pharmacokinetic properties. Compared with UH, LMWHs produce less bleeding in experimental animals for an equivalent antithrombotic effect, have much higher availability because of reduced protein binding, demonstrate linear kinetics and have a longer plasma half-life.[37] The LMWHs differ from each other in molecular weight, rate of plasma clearance, dosage regimens, ratio of anti-Xa to anti-IIa activity and clinical efficacy.[37, 38] For these reasons individual LMWHs should be considered "distinct and separate compounds."[39]

Prophylaxis of Venous Thromboembolism Following Total Hip Replacement Surgery

The use of warfarin and UH in hip surgery patients has been shown to reduce the incidence of DVT and PE.[40, 41] The Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommended warfarin (INR 2.0 to 3.0), low molecular weight heparins (LMWHs), and adjusted dose UH (started preoperatively) as effective prophylactic agents in THR patients.[10] However, prophylaxis with adjusted dose UH has been pronounced "impractical for routine use" due to frequent dosage adjustments required. The conference concluded that other agents (low dose UH ± dihydroergotamine, dextran, ASA, elastic stockings and intermittent pneumatic compression alone) were less effective, although some authors may recommend them for selected patients.[10, 42] The use of mechanical devices such as elastic stockings and intermittent pneumatic compression, in addition to drug prophylaxis, has been suggested to possibly improve efficacy.[10, 43]

In spite of these and earlier recommendations, as well as published cost-benefit analyses,[14, 44-46] thromboprophylaxis is not a common practice. Three surveys have evaluated prophylactic practices in American hospitals. In 1985, warfarin or adjusted dose UH were used in only 36% of THR patients defined by physicians as "high risk."[47] In a retrospective review of high-risk patients discharged in 1985 and 1986, only 39% of orthopedic patients received prophylaxis.[48] The authors noted that prophylaxis of high risk patients was more common in teaching hospitals (44%) and that the use of prophylaxis increased with the number of patient risk factors. More recently, an increase in the use of prophylax to 52% of eligible patients has been noted.[49]

Bleeding has been noted as a common side effect of warfarin therapy. Many patients have not received prophylaxis with warfarin or other drugs due to concerns of possible complications.[41, 47, 50] However, the lower dose warfarin currently recommended (targeted INR 2.0 to 3.0) carries a low risk

Table VI. Diagnostic Tests to Confirm Proximal DVT in Symptomatic Total Hip Replacement Patients[11, 28]

Test	Sensitivity	Specificity
Contrast venography	standard for comparison	standard for comparison
^{125}I-Fibrinogen scanning *	45%	95%
Impedance plethysmography	22%	98%
Doppler ultrasonography †	88%	88%
Colour Doppler ultrasonography †	97%	97%
Real-time B-mode or duplex ultrasonography †	97%	97%

* no longer available
† includes patients undergoing procedures other than total hip replacement.
Sensitivity indicates the proportion of patients with the disease or condition who have a positive test and has been called the true positive rate. Specificity indicates the proportion of patients without the disease or condition who have a negative test and has been called the true negative rate.

of bleeding in comparison with the higher doses previously used (targeted INR 2.5 to 4.5).[10, 51, 52] Very low dose warfarin administration (1 mg daily) has produced a low rate of adverse events, but has proven to be ineffective in THR patients.[53]

Warfarin and LMWHs — Efficacy in Thromboprophylaxis

In 1967, Harris et al demonstrated that warfarin was an effective thromboprophylactic agent in THR patients.[54] Unfortunately, diagnosis was made by clinical signs and symptoms only. In a later trial using blinded venographic assessment, Harris et al found warfarin, ASA and dextran significantly more effective than UH, although proximal thrombi were more frequent with ASA and dextran.[40] In these two trials the dose of warfarin was 10 mg on the night prior to surgery, 5 mg on the night of the surgery and the dosage was then adjusted to the desired level of anticoagulation (a target PT of 1.5 times the control value). A "low-intensity" administration protocol to a target INR of 2.0 to 3.0 is currently recommended for THR.[10] Although a "two-step" schedule of warfarin dosing to a pre-operative prothrombin time of 1.5 to 3 seconds greater than control, started 10 to 14 days prior to surgery has been employed,[55, 56] it would be impractical to administer in many settings. A recent analysis of trials to evaluate the initiation of prophylaxis preoperatively versus postoperatively (including warfarin and other therapies) was unable to make recommendations based on either efficacy or safety, in spite of a theoretical advantage of starting prophylaxis preoperatively.[50]

Several metaanalyses have compared warfarin and other oral anticoagulants with other prophylactic regimens, including placebo.[14, 57-59] The incidence of total DVT in the oral anticoagulant groups was 23 to 25%. Distal and proximal DVT were not reported separately, and total DVT rates between different regimens had overlapping 95% confidence intervals. For these reasons, as well as a lack of uniform study inclusion criteria and the different PE risks of distal and proximal DVT, clear conclusions cannot be reached from these metaanalyses.

Three LMWHs, dalteparin, enoxaparin and tinzaparin are currently approved in Canada for thromboprophylaxis in THR. The recommended doses for these agents (and warfarin) in THR is presented in Table VII. Several metaanalyses have evaluated trials of LMWHs and similar anticoagulants (including agents not available in Canada) in orthopedic and other surgical procedures.[57, 58, 60-65] The results indicated these agents did not consistently decrease the incidence of total DVT, proximal DVT, or PE. The 95% confidence intervals calculated for the different treatments showed considerable overlap, which demonstrates a lack of superiority for any specific agent. The results of these metaanalyses cannot be extrapolated to THR patients in Canada due to the agents used and the variety of surgical populations studied.

Randomized controlled trials of the LMWHs available in Canada have also yielded inconsistent results. Patients receiving enoxaparin developed significantly fewer total DVTs than patients receiving UH, but no decrease in proximal DVT and either a decrease or no change in major bleeding complications was observed.[66-69]

In small studies versus UH, dalteparin prophylaxis has produced no significant decrease in total DVT and either not change or a significant decrease in the incidence of proximal DVT and major bleeding.[70, 71] In one large trial, tinzaparin prophylaxis produced fewer total DVT, but patients had increased incidents of both proximal DVT and major bleeding compared with warfarin.[72]

Four clinical trials have compared a LMWH and warfarin in the prevention of venous thromboembolism after THR.[72-75] Because of differences in subjects enrolled, trial design, efficacy and safety, no firm recommendations can be made. Two cost-effectiveness studies of prophylaxis in hip replacement surgery have been published comparing enoxaparin with warfarin.[59, 65] They concluded that enoxaparin was more cost-effective, based on total DVT. However, since proximal DVT rates were not included, the results may not accurately reflect patient outcomes and costs.

Table VII. Thromboprophylactic Agents and Recommended Doses in Total Hip Replacement Surgery[10, 42, 88, 89]

Drug	Dose
Dalteparin (Fragmin®)	a) 5,000 IU SC once daily (in the evening) starting the evening before surgery; or b) 2,500 IU SC 1 to 2 hr before surgery, 2,500 IU 8 to 12 hr later, then 5,000 IU each morning
Enoxaparin (Lovenox®)	30 mg SC q12h starting within 24 hr of surgery
Tinzaparin (Innohep® formerly Logiparin®)	50 Xa IU/kg body weight SC 2 hr before surgery, then once daily
Warfarin* (Coumadin®)	10 mg po the night before surgery, 5 mg the night of surgery, then adjust dose to target INR 2.0 - 3.0

* Various dosing schedules and nomograms exist for this product. The dosing schedule presented is frequently cited in the literature, but a "night before surgery" dose may not be possible, particularly in cases where the patient is admitted to hospital on the day of surgery.

Recently, the safety of LMWHs and heparinoids has been reviewed.[76] The authors concluded there were no important differences in safety profiles of the different agents. They also stated that "due to great variability in the presentation of the data and the evaluation of blood losses and bleeding complications," double-blind, prospective clinical trials comparing agents would be required before recommendations could be made. Drug regulators in France have requested randomized controlled trials between different LMWHs, rather than comparisons between a LMWH and heparin or other non-LMWH prophylactic treatment, to assess outcomes and safety.[77]

Thromboembolic Risk and Duration of Postsurgical Prophylaxis

Postsurgical patients are still at risk of DVT and PE after hospital discharge. Amstutz reported that five of 1422 patients developed nonfatal PE 24 to 40 days after THR.[41] No cases were reported in an additional 793 patients who received a three-week course of oral warfarin after surgery. A British study reported thirteen cases of DVT occurring within six weeks after discharge in 50 surgical patients.[78] In a European randomized trial in THR in which oral anticoagulation was discontinued upon hospital discharge, PE occurred in three of 55 patients (5%) after discharge.[79] The author recommended three months of oral anticoagulation after hip replacement surgery.

Trowbridge et al evaluated 38 THR patients after hospital discharge using bilateral duplex ultrasonography and clinical evaluation (followed by venography when DVT was suspected) at monthly intervals for three months.[80] Two patients were diagnosed with DVT within the first month. Both were receiving subcutaneous heparin 5,000 units every 12 hours and one patient had clinical symptoms of DVT. Two additional DVT were diagnosed during the second month in asymptomatic patients who were receiving no prophylaxis; one of these DVTs occurred on the nonoperative side. The authors commented that the small sample size and the noninvasive screening test may have underestimated the actual incidence of DVT, but suggested the risk period was at least two months and that continued prophylaxis with an effective agent was warranted. An American study followed 268 THR patients receiving adjusted dose warfarin after hospital discharge for 12 weeks and reported no fatal PE during the six-month period after the surgery.[81] Trials are currently underway to further define the benefits and risks of extended prophylaxis in THR patients.[10]

In conclusion, in spite of improved outcomes due in part to earlier patient mobilization after surgery, patients undergoing THR and other lower limb surgery remain at high risk for thromboembolic complications and require prophylaxis with an effective anticoagulant.[10, 42] Proximal DVTs pose a significant risk for embolization while the risk associated with distal DVTs is considered to be very low. Warfarin, LMWHs and adjusted dose UH (started before surgery) reduce the incidence of total DVT. The choice of agent should be based on efficacy, side effects, drug interactions, cost, and convenience.[10, 82] LMWHs, unlike warfarin and UH, do not require dosage adjustment based on the results of coagulation testing. Prophylaxis with warfarin and LMWHs should be started no later than 24 hours after surgery. Frequently, drug prophylaxis can be combined with mechanical prophylaxis such as graduated compression elastic stockings or intermittent pneumatic compression. These measures will decrease the incidence of DVT and PE, but no prophylactic regimen will decrease the incidence to zero.

After discharge from hospital, the patient remains at risk of DVT for several weeks, although the exact duration of risk has not been determined. Continued prophylaxis with a convenient agent, such as warfarin (target INR 2.0 to 3.0), is appropriate. There is interest in the use of LMWHs for outpatient prophylaxis, but no recommendations can currently be made concerning their use in patients undergoing THR. Pre-discharge screening can confirm a diagnosis of DVT in a symptomatic patient, but is less effective in detecting DVT, particularly distal DVT, in the asymptomatic patient. To date, no study has been published that supports pre-discharge screening as being cost-effective.

REFERENCES

1. Surgical Procedures and Treatments, 1989-90 (cat no 82-217), Statistics Canada, Ottawa, 1992.
2. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;151:933-8.
3. Creager MA, Dzau VJ. Vascular diseases of the extremities. In: Isselbacher K, ed. Harrison's Principles of Internal Medicine. 13th ed. New York:McGraw-Hill; 1994:1135-43.
4. Merli GJ. Deep vein thrombosis and pulmonary embolism prophylaxis in orthopaedic surgery. *Med Clin North Am* 1993;77:397-411.
5. Tørholm C, Broeng L, Jørgensen PS, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. A placebo controlled study. *J Bone Joint Surg [Br]* 1991;73:434-8.
6. Borow M, Goldson H. Postoperative venous thrombosis. Evaluation of five methods of treatment. *Am J Surg* 1981;141:245-51.
7. Collins R, Scrimgeour A, Yusef S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. *N Engl J Med* 1988;318:1162-73.
8. Kakkar W, Howe CT, Flanc C, et al. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969;2:230-3.
9. Sevitt S, Gallagher NG. Prevention of venous thrombosis and pulmonary embolism in injured patients: A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. *Lancet* 1959;2:981-9.

10. Clagett GP, Anderson FA Jr, Heit J, et al. Prevention of venous thromboembolism. *Chest* 1995; 108(suppl 4):S312-34.
11. Cruickshank MK, Levine MN, Hirsh J, et al. An evaluation of impedance plethysmography and ^{125}I-fibrinogen leg scanning in patients following hip surgery. *Thromb Haemost* 1989;62:830-4.
12. Lassen MR, Borris LC, Christiansen HM, et al. Heparin/dihydroergotamine for venous thrombosis prophylaxis: comparison of low-dose heparin and low molecular weight heparin in hip surgery. *Br J Surg* 1988;75:686-9.
13. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med* 1981;94(part 1):439-44.
14. Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. *JAMA* 1987;257:203-8.
15. Hartsuck JM, Greenfield LJ. Postoperative thromboembolism. A clinical study with fibrinogen and pulmonary scanning. *Arch Surg* 1973;107:733-8.
16. Philbrick JT, Becker DM. Calf deep venous thrombosis: A wolf in sheep's clothing? *Arch Intern Med* 1988;148:2131-8.
17. Doouss TW. The clinical significance of venous thrombosis of the calf. *Br J Surg* 1976;63:377-8.
18. Buller HR, Lensing AWA, Hirsh J, et al. Deep vein thrombosis: new non-invasive diagnostic tests. *Thromb Haemost* 1991;66:133-7.
19. Turpie AGG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular weight heparin (Enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med* 1986;315:925-9.
20. Lieberman JR, Geerts WH. Prevention of venous thromboembolism after total hip and knee arthroplasty. *J Bone Joint Surg [Am]* 1994;76:1239-50.
21. Lotke PA, Steinberg ME, Ecker ML. Significance of deep venous thrombosis in the lower extremity after total joint arthroplasty. *Clin Orthop Rel Res* 1994;299:25-30.
22. Hull RD, Hirsh J, Carta CJ, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 1983;98:891-9.
23. Grant BJB. Noninvasive tests for acute venous thromboembolism. *Am J Respir Crit Care Med* 1994;149:1044-7.
24. Wheeler, HB, Anderson FA Jr. Prophylaxis against venous thromboembolism in surgical patients. *Am J Surg* 1991;161:507-11.
25. Johnson R, Green JR, Charnley J. Pulmonary embolism and its prophylaxis following Charnley total hip replacement. *Clin Orthop* 1977;127:123-32.
26. Lensing AWA, Hirsh J, Buller HR. Diagnosis of venous thrombosis. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and thrombosis: basic practices and clinical practice. 3rd ed. Philadelphia:Lippincott; 1994:1297-1321.
27. Hull R, Hirsch J, Sackett DL, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. *Circulation* 1981;64:622-5.
28. Dalen JE, Alpert JS. Natural history of pulmonary embolism. *Prog Cardiovasc Dis* 1975;17:259-70.
29. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg* 1972; 104: 134-44.
30. Redman HC. Deep venous thrombosis: Is contrast venography still the diagnostic "gold standard"?[editorial]. *Radiology* 1988; 168:277-8.
31. Weinmann EE, Salzman EW. Deep-vein thrombosis. *N Engl J Med* 1995;331:1630-41.
32. Matzdorff AC, Green D. Deep vein thrombosis and pulmonary embolism: Prevention, diagnosis, and treatment. *Geriatrics* 1992;47:48-63.
33. Stewart JH, Grubb M. Understanding vascular ultrasonography. *Mayo Clin Proc* 1992;67:1186-96.
34. Hull R, Hirsh J, Sackett DL, et al. Cost effectiveness of clinical diagnosis, venography, and noninvasive testing in patients with symptomatic deep-vein thrombosis. *N Engl J Med* 1981;304:1561-7.
35. Hillner BE, Philbrick JT, Becker DM. Optimal management of suspected lower-extremity deep vein thrombosis. *Arch Intern Med* 1992;152:165-75.
36. Hirsh J. Oral anticoagulant drugs. *N Engl J Med* 1991;324:1865-75.
37. Hirsh J, Levine MN. Low molecular weight heparin. *Blood* 1992;79:1-17.
38. Fareed J, Walenga JM, Hoppensteadt D, et al. Comparative study on the in vitro and in vivo activities of seven low-molecular-weight heparins. *Haemostasis* 1988;18(suppl 3):S3-15.
39. Green D, Hirsh J, Heit J, et al. Low molecular weight heparin: a critical analysis of clinical trials. *Pharmacol Rev* 1994;46:89-109.
40. Harris WH, Salzman EW, Athanasoulis C, et al. Comparison of warfarin, low-molecular weight dextran, aspirin, and subcutaneous heparin in prevention of venous thromboembolism following total hip replacement. *J Bone Joint Surg [Am]* 1974;56:1552-63.
41. Amstutz HC, Friscia DA, Dorey F, et al. Warfarin prophylaxis to prevent mortality from pulmonary embolism after total hip replacement. *J Bone Joint Surg [Am]* 1989;71:321-6.
42. Potyk DK, Tabbarah HJ. The pathogenesis and prevention of thromboembolic complications in patients undergoing total hip replacement. *J Gen Intern Med* 1993;8:213-9.
43. Wille-Jørgensen P. Prophylaxis of postoperative thromboembolism with combined methods. *Semin Thromb Haemost* 1991;17(suppl 3):S272-7.
44. Hull RD, Hirsh J, Sackett DL, et al. Cost-effectiveness of primary and secondary prevention of fatal pulmonary embolism in high-risk surgical patients. *Can Med Assoc J* 1982;127:990-5.
45. Bergqvist D, Mätzsch T. Cost/benefit aspects on thromboprophylaxis. *Haemostasis* 1993;23(suppl 1):S15-9.
46. Hauch O, Khattar SC, Jørgensen LN. Cost-benefit analysis of prophylaxis against deep vein thrombosis in surgery. *Semin Thromb Hemost* 1991;17(suppl 3)S280-3.
47. Paiement GD, Wessinger SJ, Harris. Survey of prophylaxis against venous thromboembolism in adults undergoing hip surgery. *Clin Orthop Rel Res* 1987;223:188-93.
48. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. Physician practices in the prevention of venous thromboembolism. *Ann Intern Med* 1991;115:591-5.
49. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. Prospective study of the impact of continuing medical education and quality assurance programs on use of prophylaxis for venous thromboembolism. *Arch Intern Med* 1994;154:669-77.
50. Kearon C, Hirsh J. Starting prophylaxis for venous thromboembolism postoperatively. *Arch Intern Med* 1995;155:366-72.
51. Paiement GD, Schutzer SF, Wessinger SJ, et al. Influence of prophylaxis on proximal venous thrombus formation after total hip arthroplasty. *J Arthroplasty* 1992;7:471-5.
52. Levine MN, Raskob G, Landefeld S, et al. Hemorrhagic complications of anticoagulant treatment. *Chest* 1995;108(suppl 4):S276-90.
53. Fordyce MJF, Baker AS, Staddon GE. Efficacy of fixed minidose warfarin prophylaxis in total hip replacement. *Br Med J* 1991;303:219-20.

54. Harris WH, Salzman EW, DeSanctis RW. The prevention of thromboembolic disease by prophylacticanticoagulation. *J Bone Joint Surg [Am]* 1967;49:81-9.
55. Francis CW, Marder VJ, Evarts M, et al. Two-step warfarin therapy, *JAMA* 1983;249:374-8.
56. Francis CW, Pellegrini VD Jr, Marder VJ, et al. Comparison of warfarin and external pneumatic compression in prevention of venous thrombosis after total hip replacement. *JAMA* 1992;267:2911-15.
57. Simonneau G, Leizorovicz A. Prophylactic treatment of post-operative thrombosis. A meta-analysis of the results from trials assessing various methods used in patients undergoing major orthopaedic (hip and knee) surgery. *Clin Trials Metaanal* 1993;28:177-91.
58. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. *JAMA* 1994;271:1780-5.
59. Menzin J, Colditz GA, Regan MM, et al. Cost-effectiveness of enoxaparin vs low-dose warfarin in the prevention of deep-vein thrombosis after total hip replacement surgery. *Arch Intern Med* 1995;155:757-64.
60. Anderson DR, O'Brien BJ, Levine MN, et al. Efficacy and cost of low-molecular-weight heparin compared with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. *Ann Intern Med* 1993;119:1105-12.
61. Borris LC, Lassen MR, Jensen HP, et al. Perioperative thrombosis prophylaxis with low molecular weight heparins in elective hip surgery. Clinical and economic considerations. *Int J Clin Pharmacol Ther* 1994;32:262-8.
62. Breyer HG. Thromboprophylaxis with heparin and low molecular weight heparin in elective hip surgery: Current status and perspectives. *Semin Thromb Haemost* 1991;17:336-42.
63. Lassen MR, Borris LC, Christiansen HM, et al. Clinical trials with low molecular weight heparins in the prevention of postoperative thromboembolic complications: a metaanalysis. *Semin Thromb Haemost* 1991;17(suppl 3):S284-90.
64. Leizorovicz A, Haugh MC, Chapuis FR, et al. Low molecular weight heparin in prevention of perioperative thrombosis. *Br Med J* 1992;305:913-20.
65. O'Brien BJ, Anderson DR, Goeree R. Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after hip replacement. *Can Med Assoc J* 1994;150:1083-90.
66. Colwell CW, Spiro TE, Trowbridge AA, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. *J Bone Joint Surg [Am]* 1994;76:3-14.
67. Spiro TE, Colwell CW, Trowbridge AA, for the Enoxaparin Clinical Trial Group. A clinical trial comparing the efficacy and safety of enoxaparin a low molecular weight heparin and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement surgery [abstract]. *Blood* 1992;80(suppl): S167a.
68. Le Balc'h T, Landais A, Butel J, et al. Enoxaparine (Lovenox®), versus standard heparin in prophylaxis of deep vein thrombosis (dvt) after total hip replacement (thr) [abstract]. *Thromb Haemost* 1987;58:241.
69. Levine MN, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis after elective hip surgery; A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991; 114:545-51.
70. Potron G, Barre J, Droulle C, et al. Thrombosis prophylaxis with low molecular weight heparin (Kabi 2165) and calcium heparin in patients with total hip replacement [abstract]. *Thromb Haemost* 1987;58:118.
71. Eriksson BI, Kälebo P, Anthmyr BA, et al. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement. *J Bone Joint Surg [Am]* 1991;73:484-93.
72. Hull R, Raskob G, Pineo G, et al. A comparison of subcutaneous low-molecular weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. *N Engl J Med* 1993;329:1370-6.
73. Gerhart T, Yett H, Donovan A, et al. Organon 10172 vs. Warfarin to prevent venous thrombosis after hip fracture [abstract]. *Thromb Haemost* 1987;58:240.
74. Heit J, Kessler C, Mammen E, et al. Efficacy and safety of RD heparin (a LMWH) versus warfarin after hip or knee replacement [abstract]. *Blood* 1991;78(suppl):S187a.
75. The RD Heparin Arthroplasty Group. RD Heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. *J Bone Joint Surg [Am]* 1994;76:1174-85.
76. Borris LC, Lassen MR. A comparative review of the adverse effect profiles of heparins and heparinoids. *Drug Safety* 1995;12:26-31.
77. Planes A, Chastang C, Vochelle N, et al. Comparison of antithrombotic efficacy and haemorrhagic side-effects of reviparin-sodium versus enoxaparin in patients undergoing total hip replacement surgery. *Blood Coagul Fibrinolysis* 1993;4(suppl I):S33-5.
78. Scurr JH, Coleridge-Smith PD, Hasty JH. Deep vein thrombosis: a continuing problem. *Br Med J* 1988;297:28.
79. Swierstra BA, Stibbe J, Schouten HJA. Prevention of thrombosis after hip arthroplasty. *Acta Orthop Scand* 1988;59:139-43.
80. Trowbridge A, Boese CK, Woodruff B, et al. Incidence of posthospitalization proximal deep venous thrombosis after total hip arthroplasty. *Clin Orthop Rel Res* 1994;299:203-8.
81. Paiement GD, Wessinger SJ, Hughes R, et al. Routine use of adjusted low-dose warfarin to prevent venous thromboembolism after total hip replacement. *J Bone Joint Surg [Am]* 1993;75:893-8.
82. Lukinuk C, Perks B, Rasymas A, Tom E. Alternative therapeutic charts [letter]. *Can J Hosp Pharm* 1995;48:326-7.
83. Haake DA, Berkman SA. Venous thromboembolic disease after hip surgery. *Clin Orthop Rel Res* 1989;282:212-31.
84. Kottke-Marchant K. Laboratory diagnosis of hemorrhagic and thrombotic disorders. *Hematol Oncol Clin North Am* 1994;8:809-53.
85. Lassen ML, Borris LC, Christiansen HM, et al. Prevention of thromboembolism in 190 hip arthroplasties. *Acta Orthop Scand* 1991;62:33-8.
86. Harris WH, Salzman EW, Athanasoulis C, et al. Aspirin prophylaxis of venous thrombosis after total hip replacement. *N Engl J Med* 1977;297:1246-9.
87. Leclerc JR, Geerts WH, Desjardins L, et al. Prevention of deep vein thrombosis after major knee surgery - A randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. *Thromb Haemost* 1992;67:417-23.
88. Gillis MC, editor. CPS. Compendium of Pharmaceuticals and Specialties. 31st ed. Ottawa:Canadian Pharmaceutical Association;1996.
89. Pharmacia Inc. Fragmin Product monograph. Mississauga; 1994:November.