VENOUS THROMBOEMBOLISM AFTER TOTAL HIP ARTHROPLASTY
A REVIEW OF INCIDENCE AND PREVENTION
DURING HOSPITALIZATION AND AFTER HOSPITAL DISCHARGE

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The efficacy of in-hospital prophylaxis against venous thromboembolic disease after elective total hip arthroplasty is well documented in the literature. Low-molecular-weight heparins, early ambulation, and the arterio-venous impulse system foot pump have been accepted as an efficacious form of prophylaxis against deep venous thrombosis after total hip arthroplasty. Consequently, orthopedic surgeons generally use pharmacologic or mechanical methods, or both, as prophylaxis against this complication. In contrast, there has been recent debate in the literature concerning the options for prophylaxis against venous thromboembolic disease after hospital discharge. Various approaches have been suggested and are being used in daily clinical practice. One option is to screen all patients routinely with ascending venography before discharge from the hospital; another option is to screen all patients routinely with duplex ultrasonography before discharge from the hospital; finally, extending pharmacologic prophylaxis with a low-molecular-weight heparin for at least 3 weeks after hospital discharge might be justified. Recently, this issue was further addressed in a Belgian multicenter trial confirming a potential benefit for continued low-molecular-weight heparin prophylaxis after hospital discharge, especially when patients have a limited mobility.

Keywords: deep venous thrombosis; total hip replacement; prevention.
Mots-clés: thrombose veineuse profonde; prothèse totale de hanche; prévention.

INTRODUCTION

In-hospital prophylaxis against venous thromboembolic disease after total hip arthroplasty is well documented in the literature (12). Consequently, orthopedic surgeons generally use pharmacologic or mechanical methods, or both, as prophylaxis against this complication, with the goal of decreasing the prevalence of the clinical consequences. This attitude is confirmed by a recent survey among orthopedic surgeons showing that 95% of all patients managed with total hip arthroplasty receive thromboprophylaxis during hospitalization (28). In contrast, orthopedic surgeons often choose to discontinue pharmacologic prophylaxis at the time of discharge, as the optimal method for the prevention of deep venous thrombosis after hospital discharge remains a matter of controversy (10). The purpose of this paper is to describe the incidence of venous thromboembolic disease in patients managed with total hip replacement, and to review the current options for prophylaxis against this complication, both during hospitalization and after hospital discharge.

VENOUS THROMBOEMBOLISM
DURING HOSPITALIZATION

A. Incidence without prevention

Among all hospitalized patients, those under- going total hip replacement undoubtedly have a high risk of venous thromboembolism. Unless prophylactic measures are used, the overall incidence of deep venous thrombosis, as diagnosed by venography, can exceed 60%, especially if there
is a lengthy convalescence involving bed rest (13). The incidence of calf-vein thrombosis is 40 to 60% ; proximal deep venous thrombosis occurs in approximately 20 to 40% of patients ; pulmonary embolism can occur in up to 4% of the patients ; the incidence of objectively confirmed postthrombotic syndrome 36 months after surgery is 13% (12, 24).

**B. Current options for prophylaxis**

Preventing deep venous thrombosis in patients at risk is clearly preferable to treating the condition after it has appeared (23), a view that is supported by cost-effectiveness analysis (3, 11, 17, 23). Consequently, in-hospital prophylaxis against venous thromboembolic disease after total hip arthroplasty is well accepted (28). Several methods of prophylaxis have been shown to reduce the risk of venous thromboembolism. Imperiale and Speroff (12) performed a meta-analysis to determine the efficacies of the accepted methods of prophylaxis of venous thromboembolism following total hip arthroplasty and to estimate the risks of clinically important hemorrhage with each method. In their meta-analysis of 56 trials involving methods to prevent deep venous thrombosis in 7,976 patients who had a total hip replacement, Imperiale and Speroff found that low-molecular-weight heparin and warfarin were the most effective for protection from a proximal thrombus. The risk of proximal thrombosis was 5% in patients who had been managed with warfarin and 6% in patients who had been managed with low-molecular-weight heparin. Dextran, heparin, and intermittent pneumatic compression were also found to reduce the risk compared with the risk in the control groups, but aspirin was not effective. Although warfarin and low-molecular-weight heparin were most effective for the prevention of a proximal thrombus, they were also associated with the highest risk of clinically important bleeding (1.3% for warfarin and 1.8% for low-molecular-weight heparin). Only heparin was associated with a higher rate of bleeding complications (2.6%). Low-molecular-weight heparin was superior to all other methods for the prevention of proximal and distal thrombi (17%). Finally, those authors (12) concluded that low-molecular-weight heparin and intermittent pneumatic compression were both effective for the prevention of pulmonary embolism (0.7% for low-molecular-weight heparin and 0.7% for intermittent pneumatic compression).

Several preparations of low-molecular-weight heparins are available. Low-molecular-weight heparins share a number of properties, but they differ in profiles of the distribution of molecular weight, specific activities (measured as the ratio of factor Xa to factor IIa), rates of clearance from plasma, and recommended dosage regimens (27). Thus, it should not be assumed that all low-molecular-weight heparins have similar clinical benefits. Leizorowicz and Haugh (15) performed a meta-analysis on the data from 32 clinical trials, including a total number of 15,863 patients who had been managed with various preparations of low-molecular-weight heparins utilizing the dosage as recommended by the manufacturers. This meta-analysis included the following preparations of low-molecular-weight heparins for inhospital prevention against venous thromboembolism: Kabi 2165/dalteparin (Fraxiparin®) ; CY 216/ nadroparin (Fraxiparine®) ; CY 222, PK 10169/enoxaparin (Clexane®/Lovenox®) ; LHN-1/tinzaparin (Logiparin®/Innohep®) ; OP 2123/parnaparin (Fluxum®). This meta-analysis showed that nadroparin, adjusted according to the patient’s body weight and according to the day after surgery, was superior to all other low-molecular-weight heparins for the in-hospital prevention of both deep venous thrombosis and pulmonary embolism. Unfortunately, these data are available only in the form of a paper published in the proceedings of a symposium (15). To the best of our knowledge, however, there are no other studies directly comparing the in-hospital use of low-molecular-weight heparin, so the relative effectiveness can only be inferred from this meta-analysis (15).

Elastic stockings and intermittent pneumatic compression have been accepted as an efficacious form of mechanical prophylaxis against deep venous thrombosis after total hip arthroplasty. Nevertheless, tolerance of the device is a problem for some patients (26, 29). There is, however, no risk of major postoperative bleeding (12, 29).
Recently, Warwick et al. (26) conducted a prospective, randomized trial to compare the safety and effectiveness of the A-V Impulse System foot pump with that of low-molecular-weight heparin for reducing the prevalence of deep venous thrombosis after total hip replacement. Two-hundred-ninety patients managed with a primary total hip replacement, were randomized to receive enoxaparin for seven days after the operation or to use the foot pump for seven days. There was no difference in prevalence of deep venous thrombosis, as determined by venography on the sixth, seventh, or eighth postoperative day, between the two groups. No patient in either group had proximal deep venous thrombosis. One patient who used the foot pump had a nonfatal pulmonary embolism. There were more soft-tissue side effects in the patients who received enoxaparin than in those who used the foot pump: there was more bruising of the thigh and oozing of the wound, postoperative drainage, and swelling of the thigh. When asked about the acceptability of the device, 11% of the patients who used the foot pump said that it was uncomfortable, 17% reported sleep disturbance, and 3% stated that they had stopped using the device. Conversely, 8% found it relaxing. Warwick et al. (26) conclude that the foot pump is a suitable alternative to low-molecular-weight heparin for prophylaxis against thromboembolism after total hip replacement and that it produces fewer soft-tissue side effects. Tolerance of the device is a problem for some patients (26).

VENOUS THROMBOEMBOLISM AFTER HOSPITAL DISCHARGE

A. Incidence without prevention

Arcelus et al. (1) reviewed the natural history of venous thromboembolism in surgical patients and the influence exerted by the available prophylactic methods. In their overview analysis, Arcelus et al. (1) calculated the proportion of deep venous thromboses detected after the seventh postoperative day in patients undergoing total hip arthroplasty without prophylaxis in several studies. Overall, 21% of the total number of thrombi were detected after the first postoperative week when prophylaxis was not used. Similar results have been reported showing a late onset of pulmonary embolism when different prophylactic modalities were used (1). Moreover, there is evidence that some prophylactic modalities, especially low-dose heparin and dextran, might retard the onset of venous thromboembolism. Indeed, several studies have shown a second peak in the rate of postoperative deep venous thrombosis after discontinuing the administration of low-dose heparin or dextran. Some mechanical forms of prophylaxis have also been associated with a delay in the presentation of venous thromboembolism.

In a prospective pilot study by Trowbridge et al. (25), four of 42 patients managed with total hip arthroplasty developed deep venous thrombosis during the three months after discharge from the hospital; three of the four patients who developed deep venous thrombosis had normal bilateral venograms before discharge; two patients developed deep venous thrombosis during the first month after discharge and two during the second month. In a survey study among 19,586 primary total hip arthroplasties, White et al. (28) found that the cumulative incidence of deep venous thrombosis or pulmonary embolism within three months of surgery was 2.8%. The diagnosis of thromboembolism was made after hospital discharge in 76% of the cases, with a median time of diagnosis of 17 days after surgery. Finally, the results of an inception cohort study reported in abstract form (24) suggest that asymptomatic thrombosis carries an increased risk of late postthrombotic syndrome. In that study of patients with joint replacement followed for three years, patients who developed and were treated for asymptomatic thrombosis had six times the risk (24% incidence) of objectively confirmed postthrombotic syndrome compared with those who had no perioperative thrombosis (24).

B. Options for prophylaxis

There has been recent debate in the literature concerning the options for prophylaxis against venous thromboembolic disease after hospital discharge (10). Various approaches have been suggested and are being used in daily clinical practice.
Currently, four strategic options for prophylaxis in high-risk orthopedic patients exist: first, no in-hospital screening, and no prophylaxis or screening after hospital discharge; second, in-hospital screening with venography, and no prophylaxis after hospital discharge if the in-hospital screening is negative; third, in-hospital screening with duplex ultrasonography, and no prophylaxis after hospital discharge if the in-hospital screening is negative; fourth, no in-hospital screening, but continuation of in-hospital prophylaxis after hospital discharge.

Prophylaxis in hospital and then discharge without additional surveillance or prophylaxis, is probably the most common approach (10). This approach is supported by at least one study (22). Robinson et al. (22) showed that in patients who have undergone total hip replacement, the routine performance of screening compression ultrasonography prior to hospital discharge to identify and permit the treatment of patients with asymptomatic proximal deep venous thrombosis did not reduce the rate of subsequent symptomatic thromboembolic complications. The rate of subsequent thromboembolic complications was similar in the total hip arthroplasty patients who had a normal bilateral compression ultrasound at discharge and in those patients who underwent a sham procedure designed to mimic the technique of compression ultrasonography. On the basis of these results, routine in-hospital screening, or extending pharmacologic prophylaxis beyond ten to 14 days after surgery might not be justified.

Another option is to screen all patients routinely with ascending venography before discharge from the hospital (21). Ricotta et al. (21) performed an overview analysis evaluating the incidence of clinically overt venous thromboembolism in patients who were discharged from hospital after major orthopedic surgery with normal venogram results and without further pharmacologic prophylaxis. In 2,361 patients with normal venographic results, 30 episodes of symptomatic venous thromboembolism after hospital discharge were reported, with a resulting cumulative incidence of 1.27%. Six cases of pulmonary embolism were reported. On the basis of these results, extending pharmacologic prophylaxis does not appear to be justified in patients who have normal venogram results at the time of their discharge from the hospital (21). Standard contrast venography is still considered by many authors to represent the most accurate means of diagnosing clinically significant proximal deep vein thrombosis. Unfortunately, this test has several drawbacks, including its invasive nature, its difficulty to perform in the postoperative state, and its inconsistent intrapelvic visualization. In addition, it has allergic, nephrotoxic, and thromboembolic complications that represent a small, but significant risk (4, 5).

The routine use of duplex ultrasonography as a screening tool has gained popularity recently, because its accuracy may rival the accuracy of standard contrast venography. Its noninvasive nature, its relative ease of performance in the postoperative state, and its lack of known complications are attractive (7, 8). Duplex ultrasonography's drawbacks include technician dependence, cost, and the conflicting reports in the literature regarding the accuracy of duplex ultrasonography for the detection of asymptomatic proximal thrombi in patients who have had a total hip arthroplasty (7, 8). As a result of a normal ultrasound between the fifth and eighth postoperative day, Maloney et al. (16) discontinued pharmacologic prophylaxis in 1,524 patients who were followed for at least 6 months. During this six-month follow-up period, only 18 patients (1.2%) were confirmed to have deep venous thrombosis by ultrasound, and only one patient had a nonfatal pulmonary embolism. On the basis of their results, Maloney et al. (16) concluded that it appears to be safe to discontinue thromboembolic prophylaxis in patients who have normal duplex ultrasound results between the fifth and eighth postoperative day (16).

The efficacy and safety of routine use of adjusted low-dose warfarin for 12 weeks after surgery, without sonography or venography, for the prophylaxis of deep venous thrombosis after total hip replacement was assessed by Paiement et al. (18). Two-hundred sixty-one patients were given warfarin orally both before and after the operation. Neither phlebography nor sonography was done routinely. All patients continued to take low-dose warfarin for 12 weeks after the operation. All of the patients were followed for six months after
the operation. There were no fatal pulmonary emboli during the period of the study and no known pulmonary emboli after discharge from the hospital. No major bleeding episodes occurred after discharge from the hospital. Sixteen patients (6%) had a minor episode of bleeding, but none required treatment. On the basis of these results, Paiement et al. (18) conclude that extending pharmacologic prophylaxis might be justified in patients managed with total hip replacement.

Recently, this issue was further addressed in five randomized studies of patients receiving standard prophylaxis with a low-molecular-weight heparin (enoxaparin, dalteparine, nadroparin) continued for 3 to 4 weeks after hospital discharge (2, 6, 9, 14, 20). In the first study by Planes et al. (20), bilateral venography was performed systematically at the time of hospital discharge, and showed an overall incidence of deep venous thrombosis of 13%. After hospital discharge, only those patients without deep venous thrombosis received either enoxaparin or placebo. An additional 2.7% of the patients in the low-molecular-weight heparin group and 20% in the placebo group experienced deep venous thrombosis as demonstrated by a second venography performed at the end of the three-week treatment. In a second study by Bergqvist et al. (2), venography was performed only at the end of a one-month treatment and demonstrated thrombotic events in 18% of the patients in the enoxaparin group, versus 39% in the placebo group. A third study was designed by Dahl et al. with dalteparin (6). Venography systematically performed on the seventh postoperative day disclosed a 15.7% overall prevalence of deep venous thrombosis in patients receiving low-molecular-weight heparin. After randomization, the prevalence of deep venous thrombosis was 11.8% in the low-molecular-weight heparin group and 25.8% in the placebo group between the seventh and thirty-fifth postoperative day. In a fourth study by Lassen et al. (14), venography performed only at the end of a 35-day treatment period demonstrated thrombotic events in 4.4% of the patients in the dalteparin group, versus 11.8% in the placebo group. Finally, on behalf of the Belgian Nadroparin Post Hospital Discharge in Orthopaedics (NPHDO) Study Group, we presented the results of an open, prospective, randomized, multicenter trial at the 15th International Congress on Thrombosis (9) and also at the 1998 Annual Meeting of the Belgian Society on Thrombosis and Haemostasis. The primary objective of this multicenter study was to determine the rate of delayed venous thromboembolic complications, and the efficacy and safety of continued low-molecular-weight heparin prophylaxis CY 216/nadroparin (Fraxiparine®) during a three-week period after hospital discharge. In addition, the association between a confirmed venous thromboembolism and potentially confounding factors that influence the incidence of deep venous thrombosis after elective total hip replacement was analyzed. At hospital discharge, patients with a normal duplex scan were randomly assigned to receive continued nadroparin prevention for three weeks (n = 155) or no pharmacologic prophylaxis (n = 141). Three weeks after hospital discharge, bilateral duplex ultrasonographic screening for deep venous thrombosis was performed. In addition, the acceptability of elastic compression stockings and the compliance with the program of physiotherapy were analyzed during hospitalization and after hospital discharge. The walking ability of the patients was assessed with the use of a mobility score, on discharge and also three weeks after hospital discharge (19). The rates of deep venous thrombosis in both treatment groups were low. Overall, two patients (1.3%) assigned to the nadroparin group had deep venous thrombosis, as compared with nine patients (6.4%) assigned to receive no pharmacologic prophylaxis (p = 0.021; relative risk reduction = 79%). No significant effect was observed on either proximal or distal deep venous thrombosis with the numbers available for study. There was, however, a strong trend toward a significant difference for distal deep venous thrombosis in favor of the nadroparin group compared with the control group (p = 0.056). Symptomatic pulmonary embolism did not occur in either group. In the nadroparin group, four patients had a hematoma at the injection site, two patients had pruritis, two patients had nausea and one patient had a bleeding mouth. In the control group, one patient sustained a fracture of the other hip. There were no cases of thrombocytopenia. With the
numbers available for study, we were unable to
detect significant differences between patients with
and without deep venous thrombosis with respect
to mean age, gender, body weight, height, body-
mass index, the presence of a potential risk factor
for venous thromboembolism, type of anesthesia,
type of arthroplasty, duration of operation, du-
ration of hospitalization, perioperative blood re-
placement, surgical complications, acceptability of
elastic compression stockings, or compliance with
the physiotherapy regimen. At hospital discharge,
there was no difference in walking ability between
patients who did or did not subsequently develop
deep venous thrombosis. Three weeks after hos-
pital discharge, however, the patients who de-
veloped deep venous thrombosis were significantly
less mobile than those who did not (p = 0.018).

After elective total hip replacement, the risk of
late-onset deep venous thrombosis persists at least
until three weeks after hospital discharge. When
combined with those of previous studies, the
results of our Belgian multicenter trial support a
potential benefit for continued low-molecular-
weight heparin prophylaxis after hospital dis-
charge. Indeed, these studies all showed a relative
risk reduction of more than 50% when patients
received continued treatment with low-molecular-
weight heparin after hospital discharge. The rela-
tive risk reductions for deep venous thrombosis
overall in the studies by Planes et al. (20), Bergqvist
et al. (2), Dahl et al. (6), Lassen et al. (14), and
the NPHD-O Group (9) were 86%, 54%, 54%,
65%, and 79% respectively. Thus, it appears that
a low-molecular-weight heparin prophylaxis regi-
men after total hip replacement should be main-
tained for at least three weeks following hospital
discharge (i.e. about four to six weeks after the
surgical procedure) instead of the current seven-
to ten-day postoperative period. Our data also
indicate the need for randomized prospective
studies to evaluate the relative risk of proximal
deep venous thrombosis associated with limited
mobility after total hip arthroplasty.

REFERENCES

1. Arcelus J. I., Caprini J. A., Traverso C. I. Venous
thromboembolism after hospital discharge. Semin.
2. Bergqvist D., Benoni G., Björgell O., et al. Low-
molecular-weight heparin (enoxaparin) as prophylaxis
against venous thromboembolism after total hip replace-
3. Bergqvist D., Matzsch T., Jendteg S., Lindgren B.,
Persson U. The cost-effectiveness of prevention of post-
556, Suppl., 36-41.
Otis S. M., Walker R. H. Venous thromboembolic disease
after hybrid hip arthroplasty with negative duplex screen-
5. Beuhler K. O., D’Lima D. D., Petersilge W. J., Col-
well C. W. Jr., Walker R. H. Late deep venous thrombosis
and delayed weightbearing after total hip arthroplasty.
prophylaxis following hip replacement surgery — Results
of a double-blind, prospective, randomised, placebo-
controlled study with dalteparin. Thromb. Haemost.,
7. Grady-Benson J. C., Oishi C. S., Hanson P. B., Col-
well C. W. Jr., Otis S. M., Walker R. H. Postoperative
surveillance for deep vein thrombosis with duplex
ultrasonography after total knee arthroplasty. J. Bone
8. Grady-Benson J. C., Oishi C. S., Hanson P. B., Col-
well C. W. Jr., Otis S. M., Walker R. H. Routine post-
operative duplex ultrasonography screening and moni-
toring for the detection of deep vein thrombosis. A
9. Haentjens P. On behalf of the Belgian Nadroparin Post-
Hospital Discharge in Orthopedics Study Group
(NPHD-O). Post-hospital discharge prevention of deep
vein thrombosis with nadroparin calcium after elective
total hip replacement. Haemostasis, 1998, 28, Suppl. 2,
292.
10. Hirsh J. Evidence for the needs of out-of-hospital
1134-1135.
Cost-effectiveness of primary and secondary prevention
of fatal pulmonary embolism in high-risk surgical patients.
12. Imperiale T. F., Speroff T. A meta-analysis of methods
to prevent venous thromboembolism following total hip
13. Kudsk K. A., Fabian T. C., Baum S., Gold R. E.,
Mangiante E., Voeller G. Silent deep vein thrombosis


**SAMENVATTING**

P. HAENTJENS. Thromboembolische verwikkelingen na electieve totale heupartrotplasie. Een overzicht betreffende incidentie en preventie tijdens de hospitalisatieperiode alsook na ontslag uit het ziekenhuis.

Er bestaat ruim overeenstemming dat, na electieve totale heupartroplastiek, zowel farmacologische als fysieke middelen de incidentie van diepe veneuze trombose noemenswaardig verminderen. Vooral laag moleculair gewicht heparines, vroegtijdige postoperatieve mobilisatie en intermitterende voetzoolcompressie met de zogenaamde „arterio-veneous impulse system foot pump” geven een duidelijke antitrombotische bescherming. Ondanks overtuigende bewijzen van de geringere frequentie van diepe veneuze trombosen en longembolieën dank zij preventie tijdens de hospitalisatieperiode, staan veel chirurgen nog steeds aarzelend tegenover het verderzetten van elke vorm van profylaxe na ontslag uit het ziekenhuis. Aangezien na het verlaten van het ziekenhuis een trombo-embolisch risico bij de geopereerde patiënt blijft bestaan, worden momenteel de volgende preventieve maatregelen voorgesteld in de literatuur : een systematische visualisatie van de venen met contrastvenografie ; een systematische visualisatie van de venen met Doppler echografie ; of, een voortzetting van preventieve maatregelen zoals het dagelijks subcutaan toedienen van laag moleculair gewicht heparines gedurende minstens 3 weken na ontslag uit het ziekenhuis. Ook een recente prospectieve studie, uitgevoerd in verschillende Belgische centra, bevestigde nogmaals dat het verder toedienen van laag moleculair gewicht heparines na ontslag uit het ziekenhuis nuttig is, vooral bij geopereerde personen die slechts ten dele ambulant zijn na ontslag uit het ziekenhuis.
RÉSUMÉ


Le risque de phlébo-thrombose veineuse profonde après prothèse totale de hanche est significativement réduit par le recours à une prévention médicamenteuse et physique. Les héparines de bas poids moléculaire, la déambulation précoce et la compression de l’arcade veineuse plantaire selon un cycle répétitif («arterio-venous impulse system foot pump») apparaissent actuellement comme les plus efficaces. En milieu hospitalier, l’indication d’une prévention est de moins en moins souvent remise en question. Par contre, à la sortie de l’hôpital, la prévention est encore mal codifiée probablement en raison de la diversité des protocoles publiés. Certains ont proposé l’évaluation systématique par phlébographie ou par échographie Doppler avant la sortie de l’opéré ; d’autres ont proposé la poursuite systématique de la prévention médicamenteuse pendant une durée minimale de 3 semaines. Les résultats d’une étude prospective multicentrique effectuée récemment en Belgique confortent cette dernière attitude, et incitent à poursuivre la prévention par héparines de bas poids moléculaire, surtout chez les malades peu mobiles.