The influence of oral anticoagulation therapy on deep vein thrombosis rates four weeks after total hip replacement

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Purpose: **The purpose of this study was to assess the rate of postoperative deep vein thrombosis (DVT) as a function of oral anticoagulation therapy after total hip replacement surgery.**
Methods: **A total of 125 patients completed the study. All the patients received sequential gradient pneumatic compression over elastic stockings until hospital discharge. In addition, all the patients underwent postoperative heparin therapy followed by oral warfarin therapy, adjusted in dose to maintain a goal international normalized ratio (INR) level of 2.0 to 3.0. Warfarin therapy and compression stockings were continued for 1 month after surgery. Bilateral duplex scanning was performed 1 and 4 weeks after surgery to assess the rate of DVT.**
Results: **Nineteen of the 125 patients had DVT develop (15.2%). Of those thromboses, six (31.6%) and 13 (68%) were detected 1 week and 1 month after surgery, respectively. The rate of proximal DVT was 2.4% (3 of 125) 1 week after surgery and rose to 8.2% (10 of 122) 1 month after surgery. Most DVT cases (64%; 12 of 19) were asymptomatic. The patients in whom DVT developed had significantly lower INR values during the second to fourth postoperative weeks than did those patients without thrombosis, and no differences in INR values were found during the first postoperative week.**
Conclusion: **The risk of the development of DVT extends beyond hospital discharge in patients who undergo total hip replacement, despite a regimen of prolonged oral anticoagulation therapy. This is particularly true in patients whose INR values did not reach therapeutic range during the first postoperative month. Therefore, thrombosis prophylaxis regimens on the basis of the administration of warfarin should try to maintain INR values within therapeutic range during the entire first postoperative month to minimize the incidence of DVT. (J Vasc Surg 1999;30:813-20.)**

The risk of the development of venous thromboembolism (VTE) extends for several weeks after total hip replacement.[1-12] Untreated, VTE may result in pulmonary emboli, the chronic and debilitating post-thrombotic syndrome, and even sudden death. In addition, although VTE remains the most common reason for emergency readmissions after total hip replacement surgery (THR),[13] most patients who undergo this procedure receive prophylaxis for a limited period of 7 to 14 days. A survey conducted among US orthopedic surgeons revealed that 30% of surgeons discontinue prophylaxis when patients become ambulatory and that an additional 65% limit prophylaxis to the hospitalization period.[14]

For patients who undergo THR, there is controversy regarding the need to extend prophylaxis beyond hospital discharge. Recent randomized controlled trial results have shown that the continuation of prophylaxis with low–molecular weight heparins (LMWHs) for 3 or 4 weeks after hospital discharge reduces the 1-month rate of venographically confirmed postoperative deep vein thrombosis (DVT).[9-12] Some investigators do not support such an approach and limit the use of prophylaxis to the hospitalization period.[15-18]

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Table I. Comparison of patients who were excluded and included

	Excluded (n = 32)	*Included (n = 125)*	*P value**
Average age (years)	66.5 ± 11	62.9 ± 12	.4
General anesthesia (n)	26	104	.9
Spinal or epidural anesthesia (n)	6	21	.9
Estimated blood loss (mL)	706 ± 356	669.3 ± 280	.8
Anesthesia time (min)	144 ± 30	134 ± 23	.58
Primary THR (n)	29	115	.9
Cemented cup (n)	1	8	.35

THR, Total hip replacement surgery.
*With χ^2 test or Fisher exact test.

The purpose of this study was to assess with venous duplex scanning (VDS) the rate of DVT at 1 and 4 weeks after THR in a group of patients who underwent a combined therapy of warfarin and physical methods for 1 month after surgery.

METHODS

After signing an Institutional Review Board–approved consent form, 157 patients who were scheduled for elective primary or revision THR at the Glenbrook and Evanston Hospitals were included in the study. There were 95 female and 62 male participants, with an average age of 66 ± 11 years (range, 26 to 93 years). All the THRs were performed by one of the authors (J.C.K.), with general anesthesia used in 130 cases, epidural anesthesia used in 10 cases, and spinal anesthesia used in 17 cases. A posterior approach was used in the 145 primary and the 12 revision arthroplasties. One hundred forty-seven patients underwent placement of uncemented cup components, 10 received cemented cup components, 99 received cemented stems, and 58 received uncemented stems.

The patients were properly sized and fitted with bilateral graduated thigh-length elastic stockings (TED; Kendall, Mansfield, Mass) at hospital admission. Sequential gradient pneumatic compression devices (SCD; Kendall) were applied bilaterally during the operation. A sterile SCD sleeve was applied to the operative leg, whereas a standard sleeve was used on the contralateral limb. Elastic TED stockings were used underneath the compression SCD sleeves. This combination of methods was maintained until the patient was fully ambulatory without assistance.

The patients were administered 5000 IU twice a day of sodium heparin from the night of surgery until the prothrombin time was within the aforementioned range. A 10-mg loading dose of warfarin (Coumadin Dupont Pharma, Wilmington, Del) was started the night of surgery, with subsequent dose adjustments to achieve an international normalized ratio (INR) between 2.0 and 3.0. Warfarin therapy and TED stockings were continued for 4 weeks after surgery. INR levels were measured daily during the hospital stay, three times during the first week after discharge and twice a week thereafter for 2 weeks, for a total prophylactic period of 1 month.

With a high-resolution color scanner (Ultramark 9-HDI, Advanced Technology Laboratories, Bothell, Wash), bilateral VDS was performed by the same experienced vascular technologist before surgery and at 1 and 4 weeks after surgery. The patients were placed in a reverse Trendelenburg position at approximately a 10-degree to a 20-degree angle to examine the common femoral, superficial femoral, profunda femoral, and greater saphenous veins. The examination began at the level of the common femoral vein just below the inguinal ligament. The distal superficial femoral, popliteal, and calf veins were examined, when possible, in a dependent position with legs resting on the operator's lap. This maneuver induces vein dilation and improves vein visualization. If the patient was unable to sit, the leg was externally rotated and the test was performed in the supine position. All the veins were examined in the transverse and longitudinal views.

The abnormal examination criteria that indicated DVT included: no venous Doppler scan signals noted with respiration or augmentation maneuvers, echogenic filled vessel lumen, and the inability to compress a vein with gentle probe pressure not as the result of extravascular causes. A minimum of two criteria was required for the diagnosis of DVT. Thrombi that extended to the popliteal vein or above were considered proximal, whereas those clots that were limited to the calf were considered distal.

Sequential compression was discontinued in patients whose duplex scan examination results were positive for DVT. In addition, these patinets with DVT underwent 3 to 5 days of standard intravenous heparin therapy at therapuetic doses targeted to

Table II. Summary data on the deep vein thrombosis rate at 1 and 4 weeks after total hip replacement surgery

	1st week	*4th week (new cases)*	*Overall*
Total	4.8% (6 of 125)	10.9% (13 of 119)	15.2% (19 of 125)
Proximal	2.4% (3 of 125)	5.9% (7 of 119)	8.0% (10 of 125)
Distal	2.4% (3 of 125)	5.0% (6 of 119)	7.2% (9 of 125)

reach an activated partial thromboplastin time of 2.0 to 2.5 times control, followed by at least 3 months of warfarin therapy with a target INR level between 2.0 and 3.0.

A two-tailed Fisher exact test was used to compare proportions, and an independent *t* test was used to compare continuous variables. Statistical significance was defined as $P < .05$.

RESULTS

One hundred fifty-seven patients were initially enrolled in the study and completed the prophylactic protocol, but 32 patients were excluded from the analysis because of more than two INR results being missed during the follow-up period. Accordingly, 125 patients were suitable for analysis. The demographic characteristics of the patients who were excluded and included are detailed in Table I, and no significant differences were found between the two groups. The patients were admitted to the hospital for an average of 8.4 ± 4.2 days, and the average estimated intraoperative blood loss was 634 ± 237 mL. No patient suffered major bleeding complications at surgery or during the follow-up period that required reoperation or the withdrawal of the patient from the study. There were eight minor wound hematomas (6.4%), which were treated conservatively. The INR values of the patients with bleeding complications were not significantly higher than the INR values of the patients without bleeding complications. In addition, patients with adequate anticoagulation therapy did not have more bleeding complications than did patients with subtherapeutic anticoagulation therapy.

All the preoperative duplex examination results were negative for DVT, and the total DVT rate within the first postoperative month was 15.2% (19 of 25). Sixteen patients had thrombi located in the operated leg, two patients had thrombi in the contralateral leg, and one patient had bilateral distal thrombi. Overall, there were 10 thrombi in the left leg and nine in the right leg. Pulmonary emboli were suspected of harboring in five patients, but lung scanning results confirmed the diagnosis of pulmonary embolism in only one patient (0.08%; 1 of 125). This patient was a 93-year-old woman with asymptomatic DVT that was detected on the postoperative scan on the 28th day. No patients died during the follow-up period. To prevent selection bias, we compared the DVT rate of the patients who completed the study (15%) with the DVT rate of those who were excluded from the study for missing INR values (12.5%), and no significant differences were found ($P = .9$).

Table III. Distribution of deep vein thrombosis symptoms and location with regard to day of diagnosis

Diagnosis	*Symptomatic DVT*	*Asymptomatic DVT*
Day 7 scan	1 of 125 (0.8%)	5 of 125 (4%)
Proximal	1	2
Distal	0	3
Day 28 scan (new cases)	6 of 119 (2.5%)	7 of 119 (7.5%)
Proximal	2	5
Distal	4	2
Overall DVT in 4 weeks	7 of 125 (5.6%)	12 of 125 (9.6%)
Proximal	3	7
Distal	4	5

DVT, Deep vein thrombosis.

In regards to time of occurrence and location of thrombi (Table II), VDS detected DVT in 4.8% (6 of 125) of patients on the scan on the seventh postoperative day. Of these thrombi, 50% (3 of 6) were proximal and 50% (3 of 6) were distal. On the duplex scan at the fourth week, 13 additional cases of DVT were detected (11%; 13 of 119). Of these thrombi, 54% (7 of 13) were proximal and 46% (6 of 13) were distal.

Table III describes the overall distribution of thrombi detected in the study according to whether a patient was symptomatic or asymptomatic at the time of DVT diagnosis and whether the DVT was proximal or distal. Overall, 37% (7 of 19) of the patients with a thrombus detected on VDS had symptoms of DVT (swelling, redness, tenderness, heaviness, or pain), whereas 63% (12 of 19) were asymptomatic for DVT. Two patients with positive scan results at 1 week in the calf and common femoral vein had complete DVT resolution by the 28th day. The other 17 patients with DVT had some degree of improvement.

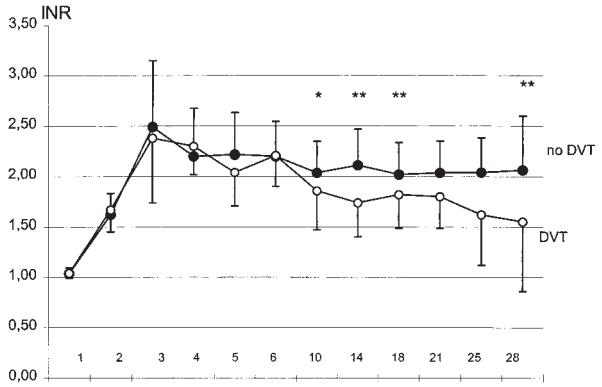

Fig 1. Mean international normalized ratio *(INR)* values in the first four postoperative weeks after total hip replacement surgery. *Open circles* indicate INR values of patients with deep vein thrombosis, and *solid circles* indicate INR values of patients without deep vein thrombosis.
**P* < .05, with *t* test.
***P* < .01, with *t* test.

Table IV compares the demographic characteristics of the patients who did and did not have DVT develop. There were no statistically significant differences between both groups of patients in regards to the distribution of age, the type and length of anesthesia, the estimated blood loss, revision THR, and the use of cemented components.

The average INR values of patients with and without postoperative DVT are shown in Fig 1. The INR values were significantly higher in the patients without DVT than in the patients with DVT during the second, third, and fourth postoperative weeks. During the first week, there were no significant differences between the two groups of patients.

The average number of days that were necessary to achieve an INR of 2.0 or more was 3.15 in the group without thrombosis and 3.66 in the group of patients in whom DVT developed ($P = .85$). Table V details the proportion of patients with an INR of 2.0 or higher during the 1-month therapy period. The proportion of patients with a therapeutic (2.0 to 3.0) INR is significantly higher in the patients without DVT as compared with the patients with DVT after the 10th postoperative day. The proportion of patients with a therapeutic INR value reached a maximum on the sixth postoperative day, with a noticeable proportional reduction on the 10th postoperative day. This could reflect superior monitoring of warfarin dosing in the hospital as compared with after hospital discharge.

Table VI shows the proportion of INR results that were within therapeutic range (2.0 to 3.0) during each postoperative week. The proportion of patients within therapeutic range was significantly higher in patients without DVT than in patients with DVT during the third and fourth postoperative weeks.

DISCUSSION

Patients who undergo THR are exposed to a high risk of the development of thromboembolic complications when preventive measures are not implemented. Although it is generally believed that most VTE appear during the early postoperative period, there is growing evidence that VTE frequently occurs after hospital discharge in surgical patients.[9-12,19] This issue has received increasing attention in recent years at both the International Consensus Conference on VTE prevention[20] and the fifth American College of Chest Physicians (ACCP) Consensus Conference.[21]

Four recent European studies have shown that the prolonging of anticoagulation therapy with the use of LMWH for 4 or 5 weeks after THR significantly reduces the rate of DVT as detected with venography.[9-12] Bergqvist et al[10] have reported a significant reduction in the proximal DVT rate in patients who undergo THR from 24% in the group receiving enoxaparin during hospital stay followed by placebo to 7% in patients who received enoxaparin for 1 month after surgery. There were two episodes of pulmonary embolism in the placebo group, and none in the group receiving prolonged enoxaparin. In a study with a similar design by Planes et al,[11] the total DVT rate was reduced from 19% to 7% with the prolonging of the use of enoxaparin for as much as 3 weeks after discharge. On the other hand, these authors did not find significant differences regarding the rate of proximal DVT with and without the prolonging of prophylaxis with enoxaparin.

Although the preliminary data on LMWH are mounting, warfarin therapy is still the preferred method of postoperative prophylaxis after hospital discharge for patients who undergo THR because it has been shown to reduce the incidence of postoperative DVT and fatal pulmonary embolism.[5,14,22,24-27] For these reasons, our approach to VTE prophylaxis consisted of a combination of elastic stockings, intermittent pneumatic compression, and adjusted subcutaneous heparin therapy during hospitalization followed by oral warfarin therapy extending to 4 weeks after surgery.

The overall rate of bleeding complications found in our study was low (6.4%), and, more importantly, none of the patients had severe enough hemorrhagic

Table IV. Comparison of patients with and without DVT

	DVT (n = 19)	*No DVT (n = 106)*	*P value**
Average age (years)	65.8 ± 11	64.2 ± 12	.54
General anesthesia (n)	16	88	.4
Spinal or epidural anesthesia (n)	3	18	.4
Estimated blood loss (mL)	733 ± 292	666.3 ± 298	.33
Anesthesia time (min)	143 ± 25	141 ± 30	.79
Primary THR (n)	18	97	.9
Cemented cup (n)	0	8	.35

DVT, Deep vein thrombosis; *THR,* total hip replacement surgery.
*With χ^2 test or Fisher exact test.

Table V. Comparison of the proportion of patients with international normalized ratio values of 2.0 or higher during the first postoperative month with patients with and without deep vein thrombosis

	Percent of patients with INR > 2		
Postoperative day	*No DVT*	*DVT*	*P value**
1	0	0	1
2	0	0	1
3	78%	77%	.8
5	75%	61%	18
6	83%	76%	.5
10	56%	35%	.18
14	62%	22%	.003
18	63%	22%	.002
21	58%	33%	.08
25	62%	11%	<.01
28	59%	11%	<.01

INR, International normalized ratio; *DVT,* deep vein thrombosis.
*With Fisher exact test.

Table VI. Proportion of patients with international normalized ratio values within therapeutic range during the first postoperative weeks and duplex scan outcome

	Percent of patients with INR between 2.0 and 3.0		
Postoperative week	*No DVT*	*DVT*	*P value**
First	41%	40%	.97
Second	40%	28%	.25
Third	61%	27%	<.001
Fourth	61%	11%	<.001

INR, International normalized ratio; *DVT,* deep vein thrombosis.
*With χ^2 test.

problems develop to necessitate blood transfusion or reoperation. Several studies have reported similar rates of bleeding problems with the use of warfarin therapy after THR.[27,40,41,44] A number of factors could be responsible for the low rate of bleeding complications found in this study. First, preoperative anticoagulation therapy was not instituted, which could explain the lack of excessive intraoperative bleeding. In addition, all the patients underwent operation by the same highly experienced orthopedic surgeon (J.C.K.). Lastly, few patients had an INR level more than 3.5 and none of the patients had an INR of more than 5. The low prevalence of bleeding problems in combination with the high rate of DVT found in this study could reflect an overly conservative approach to anticoagulation therapy, especially after the 10th postoperative day, as shown by the high proportion of patients with subtherapeutic INR levels. A recent study that compared two regimens of warfarin therapy found more bleeding complications with a more aggressive approach consisting of warfarin therapy beginning 2 weeks before surgery as compared with the night before surgery.[46]

The total DVT rate of 15% within the first postoperative month is concerning because it far exceeded the rate found at discharge (4.8%), which suggests that an extended prophylaxis protocol was unable to prevent the development of 13 new thrombi after hospital discharge. However, it is important to note that none of the patients had a fatal pulmonary embolus develop within 1 month after THR and that the total mortality rate during the study was 0%. In this regard, recent studies are revealing a low mortality rate after THR in patients who undergo different prophylactic methods.[22,25,37-39]

Because the DVT rate was low initially (4.8%), a combined prophylactic protocol appears to be effective during the first week of prophylactic therapy, especially regarding proximal clots (2.4%). Similar venographic results confirmed rates that have been reported at 1 week in patients who undergo therapy with enoxaparin.[28,29] Similarly, Tremaine et al[6] followed a group of 20 patients who underwent THR who received LMWH while in the hospital and per-

formed VDS 1 and 3 weeks after surgery. No clots were found on the 1-week scan, and eight clots (40%) were found on the 3-week scan, with only two of these cases with symptoms of DVT.

The high proportion of asymptomatic cases (36%) detected in this study was surprising. In our opinion, these results emphasize the value of VDS after THR to detect asymptomatic proximal clots, which could cause pulmonary emboli, sudden death, or the post-thrombotic syndrome. For example, Ascani et al[36] found a 28% DVT rate after THR, with all cases being asymptomatic. Furthermore, 30% of those asymptomatic thrombi were occluding the common femoral vein and 45% were considered proximal.[36] Therefore, the clinical follow-up examination of patients after THR is not accurate for the diagnosis of DVT, and the long-term impact of asymptomatic DVT after THR remains to be elucidated in further prospective studies with objective evaluation of the development of chronic venous insufficiency.

Similar to other studies, significant differences in the INR results between patients with and without DVT during the first postoperative week were not found in this study.[40,41] This might reflect the difficulty in achieving the targeted INR range during the first days of treatment. A recent study has reported that 23% of patients who undergo warfarin therapy have a lower level of anticoagulation than the target range at the time of hospital discharge.[27] If reagents that are relatively insensitive to depletion of factors II and X are used, warfarin monitoring on the basis of the INR may be unreliable during the first days of treatment.[42] The INR values were significantly higher during the second to fourth postoperative weeks in patients in whom VTE did not develop, and there was a noticeable reduction in the proportion of patients with INRs of 2.0 or higher after the 10th postoperative day (Table V). These results suggest that effective warfarin monitoring and dose adjustment may be more difficult after hospital discharge, decreasing the overall efficacy of post-discharge VTE prophylaxis.

Despite the evidence favoring extended prophylaxis, some investigators are reluctant to routinely implement prophylaxis beyond discharge, especially if a duplex scan examination result is normal before discharge.[15-18,23] The role of VTE screening after THR remains controversial. Ultrasound scanning has limitations for the detection of asymptomatic DVT[30,31] and is less accurate than venography for DVT screening after THR.[32] However, high resolution color duplex scanning performed by experienced personnel achieves a good sensitivity for the detection of proximal DVT in these cases and is used by several investigators.[8,23,26,33,34] VDS was used in this study because we did not consider it appropriate to perform two sets of venograms within 1 month in patients at high risk. Recent studies showed that more than 20% of venographic results were considered inadequate, indicating that the gold standard venogram has its own limitations.[28,35] It is important to note that both duplex ultrasound scanning and venography are coincident in documenting a significant number of DVT cases that develop after hospital discharge in many of the aforementioned studies. Lastly, there is also controversy in regards to which pharmacologic agent should be instituted for post-discharge prophylaxis. Warfarin therapy is inexpensive and well accepted by patients, which makes it an attractive method for VTE prevention after THR. However, the overall cost of the use of warfarin therapy is increased by the relatively high DVT rates reported with its use and the need to monitor INR levels for dose adjustments. Some studies have reported a small reduction in the incidence of DVT with LMWHs as compared with warfarin, but LMWHs are associated with more bleeding complications.[40,41,43,44]

This study suggests that the combination of physical methods and unfractionated heparin therapy followed by warfarin therapy for 1 month after total hip arthroplasty can result in a low rate of symptomatic DVT and pulmonary embolism if a therapeutic level of anticoagulation therapy is maintained for at least 4 weeks after surgery. However, an overall DVT rate of 15.2% at 1 month after THR, and especially an 8% proximal DVT rate, are still unacceptably high. Further prospective and randomized studies are warranted to assess the real advantages of prophylaxis after hospital discharge and to investigate the best available, most cost-effective options and the appropriate duration of prophylaxis needed to safely treat patients after total hip arthroplasty.

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DISCUSSION

Dr Russell D. Hull (Calgary, Alberta, Canada). This discussion was not rehearsed. I saw the paper, but I did not see the questions. This is work in progress from a large double-blind randomized trial that will be reported in detail at subsequent meetings. It has been reported in brief at the American Association of Hip and Knee Replacement Surgeons. This was a study of warfarin sodium administered in the hospital for 6 days as compared with low–molecular weight heparin therapy where low–molecular weight heparin was given in close proximity to the surgery. What was different with the low–molecular weight heparin regimens, and this was with dalteparin, was going within 2 hours before surgery, which is heresy in North America. We did this while going not closer than 4 hours after surgery (actually an average time of 6 hours just after surgery), which is quite different from the 18 to 24 hours or 12 to 24 hours with other regimens. So, it was dalteparin given very close to surgery versus warfarin the night of the day of surgery. On day 6, the proximal rates were 0.8% in the preoperative dalteparin regimen, 0.8% in the postoperative, and 3% in the warfarin. The total rates were 10.7%, 13.1%, and 24%. So, the first question that we have answered is that low–molecular weight heparin given very close to surgery is more effective than warfarin sodium given the evening of the day of surgery. These rates are extraordinarily low, and the regimen we used was different to that used traditionally in North America. I will not pursue that now.

The next issue is whether prophylaxis is needed in North America. We discharged patients early. There is strong division in opinion. Many argue that it is not worth pursuing prophylaxis out of hospital. We anticipated that we would do better with low–molecular weight heparin than with warfarin in hospital. We believed that there was no point in pursuing warfarin out of hospital, so it was stopped at hospital discharge. The overall rates with venography are 36%, a proximal deep vein thrombosis rate of 9.2%. Very close to what you would have predicted.

If you look at the modified regimen with dalteparin, you will see a proximal rate for pre of 3.1% and a proximal rate of 2%. These are obviously different with clinical statistical significance.

So, in answer to your two questions, modifying the regimen of dalteparin improves the thrombosis rates after surgery by reducing the proximal thrombosis rate. In hospital and in North America, yes, we need out of hospital prophylaxis.

Thank you.