Low-molecular-weight heparin for prevention of restenosis after femoropopliteal percutaneous transluminal angioplasty: A randomized controlled trial

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Background: **Restenosis after angioplasty is essentially due to intimal hyperplasia. Low-molecular-weight heparins (LMWHs) have experimentally been shown to have antiproliferative effects in addition to their antithrombotic properties. Their potential in reducing restenosis remains to be established. Therefore, we wanted to test the hypothesis that LMWH plus aspirin is more effective than aspirin alone in reducing the incidence of restenosis/reocclusion in patients undergoing percutaneous transluminal angioplasty (PTA) of femoropopliteal arteries. Further, different effects of LMWH in patients treated for critical limb ischemia (CLI) or claudication only should be investigated.**
Methods: **After successful PTA, 275 patients with symptomatic peripheral arterial disease (claudication or critical limb ischemia) and femoropopliteal obstructions were randomized to receive either 2500 IU of dalteparin subcutaneously for 3 months plus 100 mg of aspirin daily (n = 137), or 100 mg aspirin daily alone (n = 138). The primary end point was restenosis or reocclusion documented by duplex ultrasonography imaging at 12 months.**
Results: **Restenosis/reocclusion occurred in 58 patients (44%) in the dalteparin group and in 62 patients (50%) in the control group ($P = .30$). In a subgroup analysis according to the severity of peripheral arterial disease, we found that in patients treated for claudication, restenosis/reocclusion developed in 43 (43%) in the dalteparin group, and in 35 (41%) in the control group ($P = .70$); in patients treated for CLI, restenosis/reocclusion was significantly lower in the dalteparin group (15, 45%) than in the control group (27, 72%; $P = .01$). No major bleeding events occurred in either group.**
Conclusions: **Treatment with 2500 IU dalteparin subcutaneously given for 3 months after femoropopliteal PTA failed to reduce restenosis/reocclusion at 12 months. However, dalteparin may be beneficial in the subgroup of patients with CLI at 12 months follow-up. (J Vasc Surg 2006;44:1247-53.)**

Restenosis is a major problem after initially successful angioplasty of peripheral arteries and occurs in 35% to 50% of noniliac peripheral angioplasties ≤1 year after the procedure.[1,2] Causing necessity for further intervention, restenosis has not only clinical but also economic implications. Today, antiplatelet drugs are the treatment of choice for secondary prevention in patients with arterial occlusive disease. Aspirin or aspirin plus dipyridamole has been shown to reduce the risk of vascular occlusion after vascular procedures, especially in patients at high risk[3]; further, antiplatelet therapy leads to a 25% reduction in vascular events, including myocardial infarction, stroke, and vascular death.[3] Aspirin is therefore given routinely to patients being treated for peripheral arterial disease, usually in a dosage of 100 mg per day.

Restenosis is most commonly secondary to myointimal proliferation. Lesions have been related to residual hemodynamic abnormalities at the site of angioplasty, smooth muscle cell injury, and platelet deposition with subsequent release of platelet-derived growth factor. Experimental studies suggest that the process of cellular proliferation peaks 3 to 5 days after percutaneous transluminal angioplasty (PTA).[4] Several pharmacologic and nonpharmacologic approaches have been undertaken to improve the results of catheter-based treatment, but a breakthrough has not been achieved so far.

Low-molecular-weight heparins (LMWH) have been shown in experimental studies to have antiproliferative effects in addition to their antithrombotic properties,[5] and they have also been effective in a clinical setting. In a randomized clinical trial in patients with femoropopliteal bypass grafts, the effect of LMWH on graft patency was compared with that of aspirin and dipyridamole. Graft survival at 1 year was significantly higher in patients given LMWH, and in particular, in patients receiving femoropopliteal grafts for limb salvage.[6]

The aim of this controlled, prospective, randomized trial was to test the hypothesis that LMWH is more effective

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than aspirin alone in reducing the incidence of restenosis in patients undergoing PTA of femoropopliteal arteries. A further question of interest was to investigate effects of LMWH in patients treated for critical ischemia or claudication.

METHODS

Patients. From January 1999 to December 2004, symptomatic patients with angiographically or sonographically documented femoropopliteal >50% de novo or recurrent lesions scheduled for an interventional procedure at the Division of Angiology, University Hospital Zurich, were candidates for inclusion in the study. They were eligible if femoropopliteal angioplasty (balloon angioplasty with or without local thrombolysis and/or thrombus extraction) was primarily successful.

Exclusion criteria were nonatherosclerotic vascular disease, lesions in femoropopliteal bypass grafts, stent implantation, heparin or aspirin intolerance, anticoagulant treatment before PTA, pregnancy, life expectancy <12 months, stroke, surgery of the eye or of the central nervous system ≤6 months, proliferative diabetic retinopathy, active bleeding, hemorrhagic diathesis, renal failure, uncontrolled arterial hypertension, and unwillingness to return for follow-up.

The study was conducted in accordance with the recommendations of the Declaration of Helsinki and was approved by the local ethics committee. All patients gave written informed consent. Patients were consented the day after successful PTA and randomized immediately.

Recorded at baseline were age, sex, vascular risk factors of diabetes, hyperlipidemia, hypertension, and smoking habits; and history and current medication. The severity of the peripheral arterial disease (PAD) was classified according to Fontaine clinical stage II (claudication) or stage III/IV (rest pain and/or nonhealing ulceration/gangrene).[7]

The initial clinical examination included palpation of pulses, auscultation of bruits, pulse volume recordings, ankle systolic pressure measurement, and calculation of ankle-brachial index (ABI) at rest. Characteristics of the lesions to be treated, as detected by angiography, were recorded (stenosis/occlusion, length of lesion, run-off) and classified according to the TransAtlantic InterSocietal Consensus (TASC) classification.[7]

Laboratory tests included complete blood cell count and levels of serum creatinine, fibrinogen, glycosylated hemoglobin, cholesterol (high-density and low-density lipoprotein), and triglycerides.

Trial design and treatment. The trial design was a parallel group design, and patients were block randomized to one of two treatment arms. The randomization code was developed by using a computer random-number generator to select random permuted blocks.

Basic treatment was 100 mg of aspirin per day, starting the day before the procedure if the patient was not already taking aspirin. After a successful interventional procedure, the LMWH dalteparin (Fragmin, Pharmacia-Upjohn, Pfizer, New York, NY) was given in a subcutaneous dosage of 5000 IU once daily postoperatively for 2 days. Patients were randomized to receive thereafter, for the next 3 months, either 2500 IU dalteparin subcutaneously daily together with 100 mg aspirin orally or 100 mg of aspirin orally alone. Patients randomized to receive LMWH were instructed by a nurse in the method of self-injection. A dosage of 2500 IU of dalteparin daily given for 3 months has been shown to be safe, without causing major hemorrhagic events.[5]

Follow-up and end points. Patients were assessed the first day after the procedure and at 1, 3, 6, and 12 months by taking a history, a clinical examination (palpation of peripheral pulses, auscultation of bruits), pulse volume recordings, ankle-systolic pressure measurements, calculation of ABI, and color-coded duplex ultrasound imaging of the femoropopliteal segment. Peak systolic velocities (PSV) in the dilated segment and in the proximal normal segment were measured, and peak velocity ratio (calculated as PSV in the dilated segment divided by proximally recorded PSV) was calculated. A velocity ratio of ≥2.4 indicated a ≥50% restenosis at that site.[8] To retrieve the initially treated lesion in follow-up duplex examinations, the lesions were measured in centimeters from the femoral bifurcation. All sonographers were experienced investigators. They were blinded to the group assessment.

Patients were also asked to return at any time during follow-up in case of recurrence or worsening of symptoms.

The primary outcome measure was the occurrence of restenosis >50% or reocclusion as documented by duplex ultrasonography imaging (velocity ratio) at up to 12 months. Secondary outcome measures were clinical outcome defined as recurrence or worsening of clinical symptoms, defined as deterioration by at least one category as suggested by Rutherford,[9] and deterioration of ABI defined as decrease by >0.1.[7]

Compliance of the patients was assessed by observation of the injection site and return of medication boxes. Side effects of treatment, including bleeding or other adverse events, were recorded.

Sample size calculation and statistical analysis. For a predicted patency rate of 60% within the first year after PTA, with a 15% difference between the two treatment groups, the sample size required in each group was 138 patients to find this difference with 80% power and statistical significance at the 5% level.

For data management and analyses, the statistical software package Statview 5.0 (SAS Institute, Cary, NC) was used. Continuous variables are reported as means ± SD, and categoric variables as counts or percentages. Comparisons between the two treatment groups were made by the Mann Whitney *U* test for continuous variables and the χ^2 test for categoric variables. For the assessment of the outcome, the χ^2 test was applied. Freedom from restenosis/reocclusion according to treatment groups was plotted as Kaplan-Meier curves and differences among groups were analyzed by the log-rank test. Multivariate Cox proportional hazard analysis (stepwise backward) was used to study the association between restenosis/reocclusion and

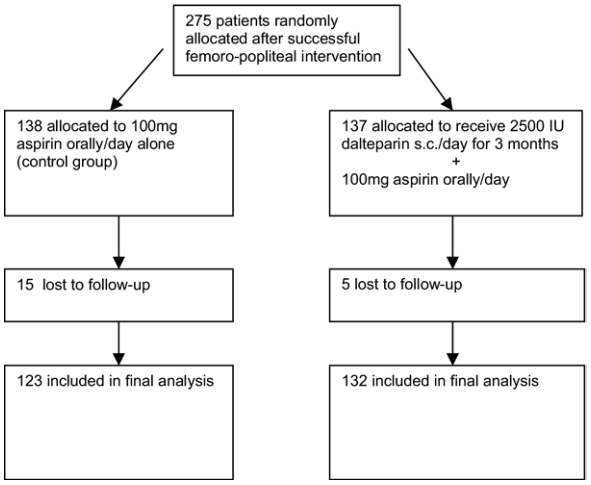

Fig 1. Flow of patients through each stage of the study.

other factors, including treatment group, lesion length, TASC class, run-off, diabetes, smoking, hyperlipidemia, hypertension, and serum creatinine, expressing the results as the hazard ratio (HR) with 95% confidence interval (CI). A value of $P < .05$ was considered to indicate statistical significance, and all tests were two-sided.

RESULTS

Patients. A total of 275 patients were recruited from January 1999 to December 2004. The flow of participants through each stage of the study is shown in Fig 1. A total of 255 patients completed the study protocol up to 12 months. The time of follow-up was 8.6 ± 4 months in the control group and 8.6 ± 4 months in the dalteparin group ($P = .98$).

From the 20 patients who did not complete follow-up, one patient was considered a protocol violator (dalteparin was terminated after 2 weeks) and 19 (7%) were lost to follow-up (8 at 1 month, 4 at 3 months, 2 at 6 months, and 5 at 12 months). Of those, 10 patients died from myocardial infarction, one from stroke, and one each from malignant disease and venous thromboembolism. No information could be obtained in six patients.

Baseline characteristics. Baseline demographic and clinical characteristics as well as laboratory variables were similar in both treatment groups (Table I and II). The groups were also similar with respect to concomitant medication, including statins, β-blockers, angiotensin-converting inhibitors, angiotensin receptor blockers, oral antidiabetic agents, insulin, and diuretic agents (all $P > .05$).

The indication for PTA was claudication in 196 patients and critical leg ischemia (CLI), defined as rest pain or nonhealing ulcer, or both, in 79 patients. These two patient subgroups, according to severity of PAD, were different with respect to female gender and diabetes, which were both more frequent in the CLI group (Table III).

Smokers were more frequent in patients with claudication. Lesion length was longer in patients with CLI, and those patients were also more likely to have occlusions than stenoses and 0-1 vessel run-off.

Table I. Baseline characteristics of the two treatment groups

*Characteristic**	*Control group n = 138 (%)*	*Dalteparin group n = 137 (%)*	P
Age (years)	70.2 ± 11	69.9 ± 10	.62
Male	60	56	.46
Diabetes	32	30	.69
Hypercholesterolemia	61	63	.70
Arterial hypertension	78	77	.88
Smoker	64	70	.24
History of coronary heart disease	42	39	.71
History of cerebrovascular disease	18	15	.62
Fontaine classification			
II	67	75	.18
III/IV	32	24	
Mean lesion length (cm)	7.8 ± 8	6.1 ± 7	.15
Total occlusion	42.7	43.4	>.99
Run-off			
0-1 vessel	38	30	.16
2-3 vessel	62	70	
TASC classification			
A	15	19	.57
B	33	34	
C	38	37	
D	14	10	
Recurrent lesions	36	30	.34
Ankle-brachial index	0.70 ± 0.18	0.66 ± 0.18	.06
Velocity ratio†	5.4 ± 1.6	5.6 ± 1.6	.24
Velocity ratio 1 day after PTA	1.24 ± 0.41	1.22 ± 0.41	.75

TASC, TransAtlantic InterSocietal Consensus; *PTA,* Percutaneous transluminal angioplasty.
*Data are shown as means ± SD or as a percentage.
†Obtained in patients with stenoses only.

Table II. Baseline laboratory values of each group

Value	*Control group (n = 138)*	*Dalteparin group (n = 137)*	P
Creatinine (μmol/L)	96.8 ± 29	96.1 ± 23	.89
Total cholesterol (mmol/L)	5.40 ± 1.3	5.45 ± 1.1	.55
HDL cholesterol (mmol/L)	1.46 ± 0.43	1.41 ± 0.42	.29
LDL cholesterol (mmol/L)	3.56 ± 1.1	3.67 ± 1.0	.25
Triglycerides (mmol/L)	1.80 ± 1.0	1.86 ± 1.1	.58
Glycosylated hemoglobin	0.074 ± 0.01	0.079 ± 0.01	.28
Hematocrit (%)	39.6 ± 4.1	39.6 ± 4.2	.61
Leukocytes ($\times 10^3/\mu l$)	8.00 ± 2.0	8.1 ± 2.7	.80
Platelets ($\times 10^3/\mu l$)	268 ± 96	262 ± 74	.79
Plasma fibrinogen (g/L)	3.76 ± 0.77	3.79 ± 0.98	.92

HDL, High-density lipoprotein; *LDL,* low-density lipoprotein.

Follow-up and outcome. Restenosis/reocclusion developed in 62 patients in the control group and in 58 patients in the dalteparin group during the 12-month follow-up, representing 50% and 44%, respectively ($P = .30$; Fig 2, *A*).

Table III. Baseline characteristics of patients treated for claudication and critical limb ischemia

*Characteristic**	*Claudication n = 196 (%)*	*CLI n = 79 (%)*	P
Dalteparin/Control group	47/53	56/44	.18
Age (years)	69.7 ± 10	70.8 ± 11	.34
Male	64	44	.002
Diabetes	25	46	.001
Hypercholesterolemia	63	57	.33
Arterial hypertension	78	77	>.99
Smoker	73	53	.002
Mean lesion length (cm)	6.1 ± 6	8.9 ± 9	.01
Total occlusion	35	62	.0001
Run-off			
0-1 vessel	28	45	.01
2-3 vessel	72	55	
TASC			
A	20	10	.059
B	34	31	
C	37	41	
D	9	18	
Recurrent lesions	37	33	.56
Ankle-brachial index	0.73 ± 0.16	0.49 ± 0.14	.0001

TASC, TransAtlantic Intersociety Classification; *PTA,* percutaneous Transluminal Angioplasty.
*Data are percentages, and means ± SD.

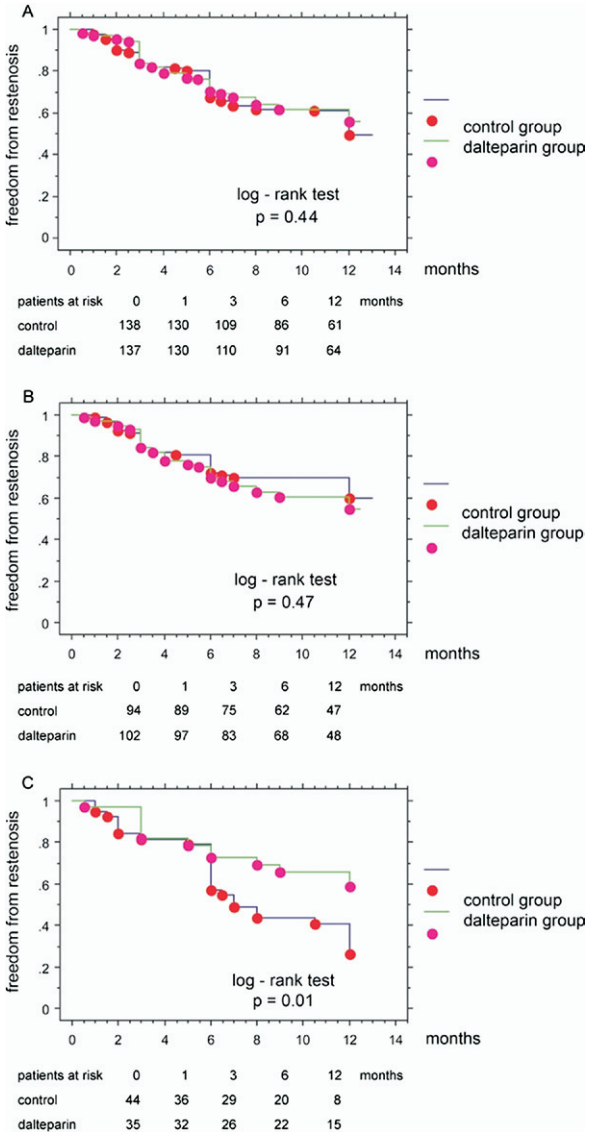

Fig 2. A, Kaplan-Meier curve for freedom from restenosis/reocclusion by treatment group (total). **B,** Kaplan-Meier curve for freedom from restenosis/reocclusion in patients with claudication by treatment group. **C,** Kaplan-Meier curve for freedom from restenosis/reocclusion in patients with critical limb ischemia by treatment group.

Subgroup analysis according to severity of PAD showed that in patients with CLI, the rate of restenosis/reocclusion was higher in the control group than in the dalteparin group (27 [73%] vs 15 [45%], $P = .01$), whereas no difference was seen in patients treated for claudication (35 [41%] vs 43 [43%], $P = .70$; Fig 2, *B* and *C*).

Rates of restenosis/reocclusion by TASC classification (A, B, C, D) were 38%, 35%, 42%, and 75% in the control group ($P = .03$), and 20%, 32%, 64%, and 41% in the dalteparin group ($P = .0008$).

Velocity ratio according to treatment groups in all patients and in the subgroup of CLI patients is shown in Fig 3, *A*. In CLI patients, velocity ratio was significantly higher in the control group than in the dalteparin group at 6 months and at 12 months ($P < .01$ each; Fig 3, *B*).

The relative incidence (cumulative) of restenosis vs rethrombosis at 12 months was 61% vs 39% in the control group and 79 vs 21% in the treatment group ($P = .03$).

PTA resulted in an increase in ABI from 0.7 ± 0.18 to 0.87 ± 0.16 ($P < .0001$) in the control group, and from 0.66 ± 0.18 to 0.89 ± 0.16 ($P < .0001$) in the dalteparin group. At 1, 3, and 12 months, ABI values were 0.88 ± 0.16, 0.86 ± 0.17, and 0.82 ± 0.19 in the control group, and 0.90 ± 0.16, 0.88 ± 0.16, and 0.88 ± 0.15 in the dalteparin group.

From a total of 120 patients with restenosis/reocclusion demonstrated by duplex ultrasonographic imaging, 102 (85%) presented with a drop >0.1 in ABI, and 89 (74%) had recurrence or worsening of clinical symptoms.

Post-hoc subgroup analysis according to the severity of PAD showed that in patients treated for CLI, recurrence or worsening of symptoms and drop in ABI were less frequent in the dalteparin group than in the control group: recurrence/worsening of clinical symptoms, 11 (33%) vs. 22 (59%) ($P = .02$); drop in ABI > 0.1, 12 (37%) vs 23 (62%) ($P = .04$).

Cox proportional hazards model. An interaction term between the treatment factors (dalteparin/control) and severity of PAD (claudication/CLI) was included into a Cox regression model and was found significant ($P = .02$). This meant that the effect of the treatment was significantly different for patients with claudication and

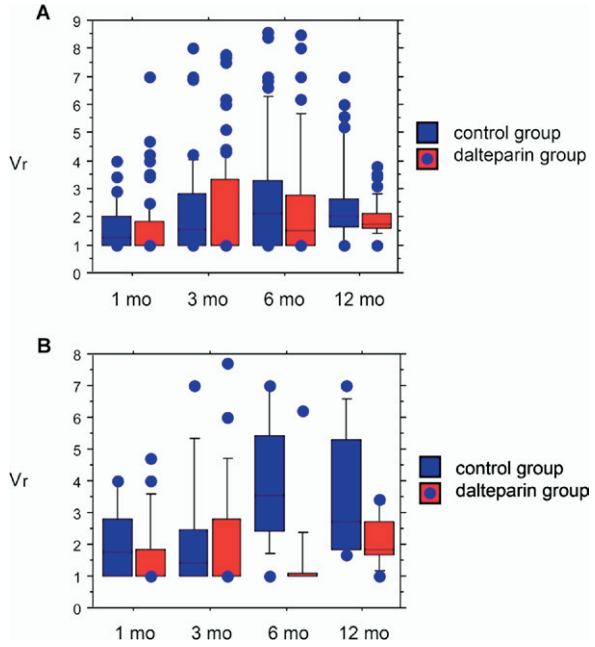

Fig 3. A, Peak velocity ratio *(Vr)* after femoropopliteal percutaneous transluminal angioplasty (PTA) in the total of patients by treatment group. **B,** Peak velocity ratio *(Vr)* after femoropopliteal PTA in patients with critical limb ischemia by treatment group. Boxes show medians (25th to 75th percentile); the blue dots represent all observations <10th or >90th percentile, respectively.

CLI. Hazard ratios were therefore calculated for claudication and CLI separately. It was found that lack of treatment with dalteparin, presence of diabetes, lesion length, and renal creatinine were associated with restenosis in patients with CLI. With a hazard ratio of 3.95, diabetes was the strongest single predictor of restenosis in CLI patients. In patients with claudication, however, lesion length and lesion morphology according to TASC were the only significant predictors for the development of restenosis/reocclusion (Table IV).

Adverse events. Special attention was paid to the occurrence of heparin-induced thrombocytopenia,[10] but neither this nor major bleeding events were observed in either group. Injection-site bruising was seen in seven patients (5.3%) in the dalteparin group; and as result, one of these patients discontinued the dalteparin medication.

Platelet count and hematocrit were not different between the control group and the dalteparin group at any point of time during follow-up. Platelets values at baseline were 266 ± 99 vs 265 ± 77; 1 day postintervention, 250 ± 100 vs 254 ± 74; 1 month, 236 ± 75 vs 259 ± 88; 3 months, 241 ± 101 vs. 251 ± 66; 6 months, 236 ± 104 vs 249 ± 75; and 12 months, 242 ± 78 vs 240 ± 69. Hematocrit values at baseline were 39.7 ± 4 vs 39.5 ± 4; 1 day, 39.0 ± 4 vs 39.0 ± 4; 1 month, 36.4 ± 4 vs 37.5 ± 3.3; 3 months, 38.5 ± 4 vs 38.7 ± 4; 6 months, 37.7 ± 3.7 vs 37.4 ± 4; and 12 months, 36.9 ± 4 vs 38.4 ± 4 (all $P > .05$).

Table IV. Multivariate Cox proportional hazards analysis*

	HR	*95% CI*	P
Claudication			
Lesion length	1.104	1.05-1.16	.0001
TASC	0.02		
1	1	—	—
2	3.45	0.92-12.9	.06
3	5.60	1.39-22.4	.01
4	5.72	1.75-18.7	.0039
Critical limb ischemia			
Treatment group	2.74	1.23-6.0	.01
Diabetes	3.95	1.6-9.7	.002
Lesion length	1.04	1.00-1.08	.01
Creatinine	0.97	0.95-0.99	.02

HR, Hazard ratio; *CI,* confidence interval; *TASC,* TransAtlantic Intersociety Classification.
*Stepwise backward.

DISCUSSION

Our study demonstrates that a regimen of 2500 IU of dalteparin administered subcutaneously daily for 3 months in addition to standard therapy with aspirin at 100 mg/d, compared with aspirin alone, offers no significant benefit for the entire cohort of patients with symptomatic PAD treated with femoropopliteal PTA. In a subgroup analysis, however, we observed a significant effect in reducing the rate of restenosis/reocclusion in patients with CLI at 12 months follow-up. In this subgroup, lack of treatment with dalteparin and the presence of diabetes were the most powerful predictors of restenosis/reocclusion, whereas in patients with claudication only, lesion morphology (according to TASC classification and lesion length) remained significant in the multivariate analysis. Therefore, patients with claudication did not seem to have an additional benefit from administration of LMWH compared with standard therapy alone.

To date, there are only few data about the effect of LMWH on restenosis after interventional procedures of peripheral arteries. In a pilot study of 42 patients,[11] reviparin (3500 IU), another LMWH, given twice a day for 23 days reduced the incidence of restenosis after stent implantation due to primarily unsuccessful PTA of the femoropopliteal segment. Furthermore, a beneficial effect of the LMWH nadroparin was suggested in patients with extensive dissection after PTA in the iliac or superficial femoral artery.[12]

To the best of our knowledge, however, ours was the first randomized and prospective study to investigate the effect of low-dose LMWH on the reduction of restenosis/reocclusion after primarily successful femoropopliteal PTA, which is by far the most often interventional procedure performed in patients with PAD.

Several trials have investigated the effect of LMWH on the incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA).[13-15] In two of those trials,[13,14] LMWH was also given for 3 months after PTCA, either in a low-dose or a high-dose scheme. In the Reduc-

tion of Restenosis After PTCA, Early Administration of Reviparin in a Double-Blind Unfractionated Heparin and Placebo-Controlled Evaluation (REDUCE) trial,[15] 3500 IU of reviparin was only administered for 28 days. No effect on the incidence of restenosis was observed. The divergence in our results in the peripheral arteries compared with the results in the coronary arteries may be explained by heterogeneity of the vasculature and by differences in the pathophysiologic mechanisms underlying restenosis in the coronary vs the femoropopliteal arteries.

According to the response-to-injury hypothesis,[16] restenosis is caused by intimal hyperplasia due to proliferation and migration of smooth muscle cells from the media into the intima. LMWH may inhibit proliferation and intimal hyperplasia.[5,17]

Another possible pathophysiologic explanation for our findings might be the anti-inflammatory effects of LMWH,[18] including its inhibitory effect on cytokines and cytokine-mediated chemotaxis[19] and on monocyte adhesion to endothelial cells.[20] This pleiotropic effect of LMWH, independent of its anticoagulatory effect, that modulates the inflammatory response, may possibly at least partly explain its benefit in patients with CLI compared with patients with claudication only. Cytokine expression in skeletal muscle has recently been associated with experimentally induced limb ischemia–reperfusion injury.[21] Furthermore, the important role of inflammation in CLI been underlined by a report showing a link between low levels of inflammatory indicators and survival rate in those patients.[22]

Of interest is that our data are virtually in complete agreement with previously published data on the effect of LMWH given for 3 months in patients undergoing femoropopliteal bypass grafting.[6] Comparable with the results of our study, the benefit of LMWH in this former study was confined to those patients undergoing surgery for CLI ("salvage surgery"). There was no significant benefit for those who had surgery for claudication. Furthermore, also in agreement with our data (see Fig 2, *C*), the benefit of LMWH in patients undergoing salvage surgery started to become evident at 3 months and was accentuated at 6 and 12 months after surgery. Obviously, the fact that CLI patients undergoing femoropopliteal PTA started to have a significant benefit from LMWH treatment 3 months after stopping therapy cannot be explained on the basis of better antithrombotic properties of LMWH. As outlined, however, both the antiproliferative and the anti-inflammatory effects of LMWH may be causally involved.

This therapy could represent an advance in the treatment of patients with peripheral vascular disease, particularly those with CLI. It still remains unclear, however, why LMWHs reduce restenosis/reocclusion in patients with CLI but do not provide a similar benefit in patients with claudication undergoing the same vascular procedure. A difference in the rates of restenosis might have partly been due to a difference in delayed thrombosis rates and may possibly provide another explanation for the benefit of a LMWH in patients with CLI. Further investigation is needed in this area before this treatment may be implemented into clinical practice.

Limitations. This prospective, randomized clinical trial was conducted as a single-center study. Although this does not necessarily imply a limitation by itself, we are aware that in other centers, for example, major centers in the United States, that practice may be different in that a higher percentage of peripheral angioplasty may have been performed with stenting. Our study was initiated in early 1999, when evidence for the use of (nitinol) stents, in particular, for the treatment of high-risk lesions in the femoropopliteal segment was still lacking. Given current knowledge and practice, however, a stent would have been implanted in more patients, in particular those with high-risk lesions. This may imply that LMWH might be of some benefit when PTA alone is used to treat such lesions.

Furthermore, clopidogrel, which is now used in a widespread fashion, was not examined in our study.

Another limitation is that for logistic reasons, this study was not placebo-controlled; however, the presence of restenosis/reocclusion was determined by ultrasonographers who were blinded with respect to the patients' treatment group.

Finally, we are aware that our finding regarding the positive effect of LMWH treatment in the subgroup of patients with CLI is somewhat hypothesis-generating, as it does not represent the true primary end point of this trial.

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AUTHOR CONTRIBUTIONS

Conception and design: RK
Analysis and interpretation: RK, SS, VR, BV
Data collection: SS, BA, TM, TP, MB, BV
Writing the article: RK, BV
Critical revision of the article: RK, SS, BA, TM, TP, VR, MB, BV
Final approval of the article: RK, SS, BA, TM, TP, VR, MB, BV
Statistical analysis: VR
Obtained funding: RK
Overall responsibility: RK

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