

# Effect of Dalteparin on Healing of Chronic Foot Ulcers in Diabetic Patients With Peripheral Arterial Occlusive Disease

A prospective, randomized, double-blind, placebo-controlled study

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outcome of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease.

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**OBJECTIVE** — Chronic foot ulcers are a common, severe, and expensive complication threatening life and limb in patients with diabetes. The aim of the present study was to investigate the effect of dalteparin on ulcer outcome in patients with diabetes, peripheral arterial occlusive disease, and chronic foot ulcers.

**RESEARCH DESIGN AND METHODS** — A total of 87 patients were investigated in a prospective, randomized, double-blind, placebo-controlled trial. Participants were randomized to treatment with subcutaneous injection of 5,000 units dalteparin (Fragmin, Pharmacia Corporation;  $n = 44$ ) or an equivalent volume of physiological saline ( $n = 43$ ) once daily until ulcer healing or for a maximum of 6 months. Ulcer outcome was investigated by evaluating the number of patients 1) who healed with intact skin; 2) in whom the study ulcer was improved, unchanged, or impaired; or 3) who were amputated above or below the ankle level, as compared with control subjects.

**RESULTS** — Two patients, one on dalteparin and one on placebo, dropped out of the study. Ulcer outcome was significantly better ( $P = 0.042$ , two-sided  $\chi^2$  test for trend) in the dalteparin group ( $n = 43$ ) compared with the placebo group ( $n = 42$ ). A total of 29 patients healed with intact skin ( $n = 14$ ) or decreased the ulcer area  $\geq 50\%$  ( $n = 15$ ) in the dalteparin group compared with 20 ( $n = 9$  and 11, respectively) in the placebo group. Five patients in each group showed impaired ulcer healing, i.e., the ulcer area increased  $\geq 50\%$ . Two patients in the dalteparin group were amputated compared with eight in the placebo group. Time to healing with intact skin was  $17 \pm 8$  weeks in the dalteparin group compared with  $16 \pm 7$  weeks in placebo group (NS).

**CONCLUSIONS** — The results of the present study indicate that dalteparin improves the

**A** rapid global increase of the incidence and prevalence of type 2 diabetes is expected, which will lead to a high number of patients with late diabetic complications. Of diabetic patients, 7–10% develop chronic foot ulcers, a severe and expensive complication threatening life and limb (1,2). Chronic foot ulcers are one of the most common reasons for hospital admissions in patients with diabetes, and almost 50% of all nontraumatic amputations are performed in diabetic patients (3). Intact local skin microcirculation and adequate arterial blood supply to the ulcer area are of crucial importance for the healing process (4). In diabetic patients with peripheral arterial occlusive disease (PAOD), the local nutritive capillary circulation is deteriorated (5), to which hemorheological disturbances might contribute. Low-molecular weight heparin (LMWH) is a potent antithrombotic agent with anti-inflammatory properties. An uncontrolled pilot study indicated that treatment with the LMWH compound dalteparin (Fragmin; Pharmacia) may positively influence skin microcirculation and ulcer healing in diabetes (6). The aim of the present study was to investigate the effect of dalteparin on the outcome of chronic foot ulcers in diabetic patients with PAOD.

## RESEARCH DESIGN AND METHODS

### Patients

From June 1997 to February 2001, 87 consecutive patients with diabetes,

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**Abbreviations:** hsCRP, high sensitive C-reactive protein; LMWH, low-molecular weight heparin; PAOD, peripheral arterial occlusive disease; S-AA, serum amyloid A-antigen; TBP, systolic toe blood pressure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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See accompanying editorial, p. 2689.

chronic foot ulcers, and PAOD were enrolled in the study. The patients were referrals for chronic foot ulcers to the Department of Endocrinology and Diabetology, Karolinska Hospital ( $n = 68$ ); the Department of Medicine, University Hospital, Lund ( $n = 6$ ); the Diabetes Center, Sahlgrenska University Hospital, Göteborg ( $n = 7$ ); and the Department of Medicine, University Hospital, Umeå ( $n = 6$ ), Sweden. The patients were randomized within each center.

#### Inclusion criteria

The inclusion criteria were foot ulcer duration of more than 2 months, ulcer stage I and II according to the Wagner classification (7), toe/arm blood pressure index  $\leq 0.6$ , and treatment with a daily dose of 75 mg aspirin for at least four weeks before randomization. Treatment with aspirin was continued in all patients during the whole study period.

#### Exclusion criteria

Exclusion criteria were vascular reconstruction or angioplasty performed less than 3 months before randomization, renal insufficiency defined as a serum creatinine level  $\geq 200 \mu\text{mol/l}$ , and treatment with anticoagulants.

#### Randomization

Eligible patients were randomized to treatment with subcutaneous injections of 0.2 ml dalteparin (Fragmin, 25,000 units/ml) or 0.2 ml physiological saline once daily until ulcer healing, or for a maximum of 6 months. The randomization list was prepared by an independent statistician by the method of computer-generated random numbers for each treatment. Patients in each stratum were assigned numbers using a central stratified randomization scheme designed to provide equal numbers of patients in each group.

#### Study medication

The study medications, i.e., dalteparin (Fragmin, 25,000 units/ml) and placebo (0.2 ml physiological saline), were kept in the local pharmacy of each hospital and dispensed as sealed packages containing injections of blinded medication. The study was double-blind, i.e., treatment assignments were concealed from the investigators, the foot care team, and the participants throughout the study.

#### Stratification

Patients were stratified for systolic toe blood pressure (TBP) and ulcer characteristics according to the Wagner classification: Stratum 1: TBP  $\geq 30$  mmHg and Wagner I; stratum 2: TBP  $< 30$  mmHg and Wagner I; stratum 3: TBP  $\geq 30$  mmHg and Wagner II; and stratum 4: TBP  $< 30$  mmHg and Wagner II.

#### Measurement of ulcer area

The ulcer area was determined in square millimeters by multiplying the largest width and length of the ulcer. The largest ulcer was considered the study ulcer when more than one ulcer was present. The measurement was performed after revision of the ulcer.

#### Procedures and patient care

All patients were treated as outpatients by a foot care team consisting of a diabetologist with special interest in angiology, a specialist diabetes nurse, a chiropodist, and an orthotist. Consultations with specialists in infectious diseases and orthopedic and vascular surgery were arranged when considered necessary. A podiatrist documented the ulcer area at baseline and then every fourth week. The foot ulcer was also documented by color photographs. Peripheral neuropathy was evaluated by investigation of pressure sensation of the foot skin to a 5.07 nylon monofilament (8) and by vibration sensation using a 128-Hz tuning fork. Non-weight-bearing protective footwear with individually fitted insoles were used by all patients. Footwear, off-loading of the ulcer(s), and compliance were inspected at each visit, and corrections were performed when required. Revision of dead and infected tissue was performed when deemed necessary. Individualized topical treatment and dressings were used depending on the site and character of the ulcer. Oral antibiotics were used in case of clinical signs of infection and were chosen according to the results of the bacterial culture and resistance pattern. Edema formation was treated with diuretics, and metabolic control and nutrition status were optimized when needed. Patients were continuously evaluated for vascular reconstruction and/or angioplasty, and investigations with angiogram and/or arterial ultrasound were performed when considered necessary. Indications for amputation were progressive gangrene and/or severe pain.

#### Discontinuation of study medication

Treatment with the study drug was stopped if ulcer healing occurred with intact skin, if the ulcer area increased by  $> 50\%$ , or if an amputation was needed. Treatment with the study drug was interrupted if conditions occurred that involved unacceptable risk with continued treatment, as judged by the physician.

#### Study objective

The primary outcome was to evaluate the effect of dalteparin on the 6-month course of chronic foot ulcers (ulcer outcome) in diabetic patients with PAOD, i.e., to determine the number of patients 1) who within 6 months after randomization had healed with intact skin; 2) in whom the study ulcer was improved, unchanged, or impaired; or 3) who were amputated above or below the ankle level, as compared with control subjects. The definition of impaired ulcer healing was an increase of ulcer area of  $\geq 50\%$ , whereas improvement was a reduction of ulcer area of  $\geq 50\%$ .

#### Peripheral circulation

Peripheral blood pressures were measured in the supine position after 20 min of acclimatization. TBP was assessed by recording the pressure (mmHg) in a miniature cuff (diameter: 2 cm) placed around the base of the great toe. The TBP was determined by evaluating the inflow of blood distal to the cuff by laser Doppler fluxmetry during deflation of the cuff (9). Systolic and diastolic arm blood pressures (mmHg) were measured by the Riva Rocci method.

#### Laboratory tests

Venous blood was taken between 8:00 and 9:00 A.M. after a 10-h fast for determination of hemoglobin, leukocyte and platelet counts, HbA<sub>1c</sub>, and serum concentrations of albumin, creatinine, high sensitive C-reactive protein (hsCRP), and serum amyloid A-antigen (S-AA). HbA<sub>1c</sub> was analyzed by an immunoturbidimetric method (UNIMATE 3 HbA<sub>1c</sub>, Roche Diagnostics), and hsCRP and S-AA were measured using particle-enhanced immunonephelometric methods (BN, Dade Behring).

#### Ethical considerations

The study protocol was approved by the local ethics committee of each center and the Swedish Medical Products Agency.

Written informed consent was obtained from the patients.

### Statistical analysis

Continuous data, such as age, diabetes duration, and biochemical variables, are reported as means  $\pm$  SD. The Student's *t* test was used to evaluate differences in continuous variables between groups. The  $\chi^2$  test was used to compare differences in distribution of categorical variables. The  $\chi^2$  exact test for trend (two-sided) was used to compare the ulcer outcome between the dalteparin and placebo group. This statistical model takes into account all study end points (healing, improvement, deterioration, and amputation) at the same time. A value of  $P < 0.05$  was considered statistically significant.

**RESULTS** — A total of 87 patients with diabetes, chronic foot ulcers, and PAOD were randomized to treatment with dalteparin ( $n = 44$ ) or placebo ( $n = 43$ ). The distribution of patients between different strata was equal regarding treatment, with fewer patients in stratum 4. Mean treatment time (i.e., time from randomization to end point) was  $20 \pm 8$  weeks in both groups.

### Dropouts

Two patients dropped out early during the study: one patient randomized to treatment with placebo suffered acute arterial thromboembolism before having the first injection of the study medication. The other patient, who was randomized to treatment with dalteparin, was excluded after 2 weeks because of an acute and painful trochanteritis, which was treated in the hospital with a daily dose of 5,000 units Fragmin (25,000 units/ml) during 4 weeks to prevent thrombosis. The ulcer healed during this period.

### Discontinuation of the study medication

The study medication was discontinued in two patients because of suspected side effects. One patient, randomized to dalteparin, got a retinal hemorrhage after 9 weeks of treatment. She was admitted for ophthalmologic investigation and recovered without any further impairment of visus. The other patient, randomized to placebo, had the study medication withdrawn because of the development of superficial skin necrosis at the site of the

**Table 1—Baseline characteristics of 85 diabetic patients with PAOD and chronic foot ulcers randomized to treatment with dalteparin or placebo**

|   | Dalteparin      | Placebo         |
|---|-----------------|-----------------|
| <i>n</i>  | 43              | 42              |
| Age (years)   | 73 $\pm$ 8      | 72 $\pm$ 11     |
| Sex (M/F)   | 29/14           | 31/11           |
| BMI (kg/m <sup>2</sup> )                            | 27 $\pm$ 5      | 26 $\pm$ 4      |
| Type 1/type 2 diabetes                              | 5/38            | 7/35            |
| Diabetes duration (years)                           | 20 $\pm$ 13     | 21 $\pm$ 14     |
| Smokers/ex-smokers/nonsmokers                       | 5/10/28         | 6/17/19         |
| Treatment with insulin/tablets/diet                 | 33/8/2          | 33/6/3          |
| Previous minor and/or major amputation              | 10              | 11              |
| Previous myocardial infarction and/or stroke        | 20              | 20              |
| Previous vascular reconstruction and/or angioplasty | 8               | 11              |
| Treatment with aspirin                              | 43              | 42              |
| TBP (mmHg)  | 53 $\pm$ 23     | 53 $\pm$ 20     |
| Toe/arm blood pressure index                        | 0.33 $\pm$ 0.14 | 0.35 $\pm$ 0.12 |
| Ulcer area (mm <sup>2</sup> )                       | 413 $\pm$ 820   | 535 $\pm$ 1,086 |
| Peripheral neuropathy                               | 43              | 42              |

Data are *n* or means  $\pm$  SD. There were no statistically significant differences between the groups.

subcutaneous injections on the belly. This patient was on insulin therapy twice daily, and the insulin injections were given within the same skin area as the study medication.

### Baseline characteristics

A total of 85 patients completed the study protocol (Table 1). Baseline characteristics of the treatment groups were comparable with an exception: more ex-smokers, defined as  $\geq 5$  years since smoking cessation, had been randomized to treatment with placebo, whereas the number of current smokers did not differ between the treatment groups. Almost 50% had a history of myocardial infarction and/or stroke, 22% had undergone vascular reconstruction or angioplasty because of leg ischemia, and 25% had an earlier amputation. A majority of the pa-

tients (78%) were on insulin treatment. All patients were treated with a daily dose of 75 mg aspirin (Trombyl, Pharmacia Corporation) for at least 4 weeks before randomization and during the study period. Foot ulcers in all 85 patients were defined as neuro-ischemic, since signs of peripheral neuropathy were present in all patients. Baseline ulcer area did not differ between the groups. One patient in the placebo group had an extremely large ulcer (measuring 6,603 mm<sup>2</sup> at baseline) that was defined as unchanged at the end point investigation. When this patient was excluded, the ulcer area in the placebo group decreased from 535 mm<sup>2</sup> (6–6,603) to 387 mm<sup>2</sup> (6–3,000) (Fig. 1).

### Ulcer outcome

The ulcer outcome—including healing with intact skin; improved, unchanged,

**Table 2—Ulcer outcome in 85 diabetic patients with PAOD and chronic foot ulcers, randomly assigned to treatment with dalteparin or placebo**

|   | Dalteparin | Placebo |
|---|------------|---------|
| <i>n</i>  | 43         | 42      |
| Healed (with intact skin)                               | 14 (33)    | 9 (21)  |
| Improved (ulcer area decreased $\geq 50\%$ )            | 15 (35)    | 11 (26) |
| Unchanged (decreased or increased ulcer area $< 50\%$ ) | 7 (16)     | 9 (21)  |
| Impaired (increased ulcer area $\geq 50\%$ )            | 5 (12)     | 5 (12)  |
| Amputation (above/below ankle)                          | 2 (5)      | 8 (19)  |
|   | 2/0        | 4/4     |

Data are *n* or *n* (%). The  $\chi^2$  exact test for trend (two-sided) showed that ulcer outcome differed significantly between the dalteparin and placebo groups ( $P = 0.042$ ).

Table 3—Baseline characteristics of 10 patients who underwent amputation

|   | Patient |       |    |     |     |       |    |     |     |     |
|---|---------|-------|----|-----|-----|-------|----|-----|-----|-----|
|   | 1       | 2     | 3  | 4   | 5   | 6     | 7  | 8   | 9   | 10  |
| Treatment                                 | D       | D     | P  | P   | P   | P     | P  | P   | P   | P   |
| Age (years)                               | 72      | 83    | 74 | 74  | 80  | 55    | 69 | 74  | 47  | 71  |
| Diabetes duration (years)                 | 1       | 23    | 23 | 11  | 25  | 10    | 3  | 30  | 39  | 18  |
| TBP (mmHg)                                | 40      | 50    | 50 | 60  | 25  | 30    | 55 | 50  | 55  | 40  |
| Ulcer area at baseline (mm <sup>2</sup> ) | 1,092   | 1,890 | 54 | 600 | 315 | 1,125 | 49 | 936 | 440 | 132 |
| Time to amputation (weeks)                | 4       | 7     | 4  | 8   | 18  | 9     | 6  | 18  | 8   | 20  |
| Site of amputation                        | A       | A     | A  | B   | B   | B     | A  | A   | A   | B   |
| hsCRP (mg/l)                              | 3       | 150   | 4  | 24  | 21  | 5     | 11 | 33  | 4   | 28  |
| S-AA (mg/l)                               | 10      | 304   | 25 | 124 | 15  | 3     | 91 | 10  | 16  | 20  |

A, above ankle; B, below ankle; D, dalteparin; P, placebo.

or impaired ulcer area; and amputation—was significantly ( $P = 0.042$ ) improved by dalteparin treatment compared with placebo (Table 2). When analyzing individual end points, there were four times more amputations in the placebo group ( $n = 8$ ) than in the dalteparin group ( $n = 2$ ; NS) (Table 3). The specific numbers of amputations in each center were as follows: Karolinska Hospital, Stockholm ( $n = 67$ ): five amputations, three above and two below the ankle, in the placebo group and one amputation above the ankle in the dalteparin group; University Hospital, Lund ( $n = 5$ ): one amputation below the ankle in the placebo group; Sahlgrenska University Hospital, Göteborg ( $n = 7$ ): two amputations, one above and one below the ankle, in the placebo group and one amputation above the ankle in the dalteparin group; University Hospital, Umeå ( $n = 6$ ): no amputations. All amputations were preceded by progressive infection and gangrene and, in some cases, severely painful ulcer(s). A total of 29 patients in the dalteparin group and 30 patients in the placebo group were treated with antibiotics. Patients in the dalteparin group who deteriorated ( $n = 7$ ) had lower ( $P < 0.05$ ) TBP ( $36 \pm 9$  mmHg) than corresponding patients in the placebo group ( $57 \pm 21$  mmHg;  $n = 13$ ). Both amputations in the dalteparin group were performed above the ankle level, whereas in the placebo group, there were four amputations above and four below the ankle level. Ulcers were divided into three groups with respect to localization. The number of patients in each group was distributed in the dalteparin and placebo group, respectively, as follows: ulcers on digits I–V ( $n = 11$  and 20);

midfoot, heel, and dorsum of the foot ( $n = 22$  and 14); and multiple ulcers ( $n = 10$  and 8). Three patients with multiple ulcers in the placebo group went to amputation, whereas in the dalteparin group, none of the patients with multiple ulcers were amputated.

More patients healed with intact skin in the dalteparin group ( $n = 14$ ) compared with the placebo group ( $n = 9$ ; NS). There was no significant difference in mean healing time between the dalteparin group ( $17 \pm 8$ ; 8–26 weeks [min–max]) and the placebo group ( $16 \pm 7$ ; 8–26 weeks [min–max]). A total of 15 patients reduced the ulcer area  $\geq 50\%$  in the dalteparin group compared with 11 in the placebo group (NS). The percentage decrease in ulcer area was the same in the dalteparin group (73%) as in the placebo group (75%). Three patients on dalteparin and one patient on placebo died in the hospital from acute myocardial infarction and/or heart failure.

Table 4—Biochemical analyses at baseline and end of study in 85 randomized diabetic patients with PAOD and chronic foot ulcers

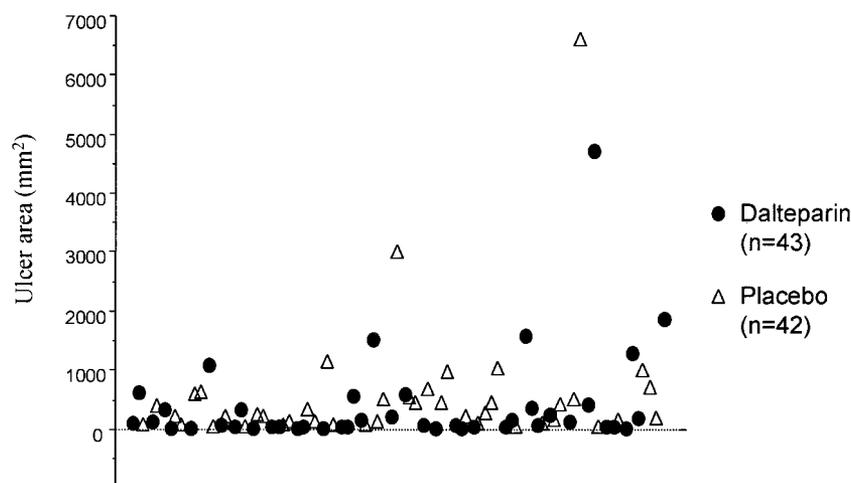
|                                  | Dalteparin    |               | Placebo       |               | P<br>(difference*) |
|----------------------------------|---------------|---------------|---------------|---------------|--------------------|
|                                  | Baseline      | End of study  | Baseline      | End of study  |                    |
| HbA <sub>1c</sub> (%)            | 6.9 $\pm$ 1.6 | 6.8 $\pm$ 1.5 | 6.9 $\pm$ 1.2 | 6.5 $\pm$ 1.1 | 0.033              |
| Hemoglobin (g/l)                 | 125 $\pm$ 15  | 125 $\pm$ 16  | 127 $\pm$ 17  | 126 $\pm$ 17  | 0.505              |
| Leukocytes ( $10^9/l$ )          | 7.6 $\pm$ 3.2 | 7.3 $\pm$ 2.3 | 8.0 $\pm$ 2.4 | 8.4 $\pm$ 2.8 | 0.966              |
| Platelets ( $10^9/l$ )           | 258 $\pm$ 72  | 278 $\pm$ 98  | 243 $\pm$ 78  | 248 $\pm$ 78  | 0.057              |
| Albumin (g/l)                    | 37 $\pm$ 3    | 37 $\pm$ 4    | 36 $\pm$ 4    | 37 $\pm$ 4    | 0.375              |
| Creatinine ( $\mu\text{mol/l}$ ) | 92 $\pm$ 23   | 97 $\pm$ 28   | 99 $\pm$ 32   | 100 $\pm$ 34  | 0.097              |
| hsCRP (mg/l)                     | 17 $\pm$ 35   | 24 $\pm$ 45   | 15 $\pm$ 24   | 14 $\pm$ 23   | 0.489              |
| S-AA (mg/l)                      | 44 $\pm$ 132  | 29 $\pm$ 61   | 32 $\pm$ 71   | 14 $\pm$ 22   | 0.949              |

Data are means  $\pm$  SD. \*Difference between dalteparin and placebo of baseline and end-of-study difference.

### Biochemical variables

There were no significant differences in hemoglobin concentration, leukocyte count, and serum concentrations of hsCRP, S-AA, albumin, and creatinine between the treatment groups at either baseline or study termination, respectively, nor were there any significant changes within the treatment groups between study termination and baseline (Table 4). At the end of the study, patients in the dalteparin group who showed a poor ulcer outcome had higher levels of hsCRP than the corresponding patients in the placebo group ( $96 \pm 101$  vs.  $17 \pm 13$  mg/l;  $P < 0.05$ ). At baseline, long-term glycemic control (HbA<sub>1c</sub>) was similar in both groups, whereas the HbA<sub>1c</sub> in the placebo group had decreased compared with baseline at the end of the study.

**CONCLUSIONS**— Treatment of diabetic foot ulcers is complicated, and healing may take several months or sometimes years (1). The impaired healing process is caused by several factors, with local ischemia due to PAOD being one of the most important (10–12). In recent years, a multidisciplinary approach including prevention, patient education, and multifactorial treatment has proven beneficial (13–15). However, to further improve the healing process and to reduce the amputation rate, new treatment strategies are urgently needed, especially because reconstructive vascular surgery or percutaneous transluminal angioplasty is not always possible. In the present study, the effect on ulcer outcome of adding dalteparin to a multidisciplinary treatment program was investigated in diabetic patients at high risk of cardiovascular com-



**Figure 1**—Ulcer area at baseline in 85 diabetic patients with peripheral arterial occlusive disease and chronic foot ulcers randomized to treatment with dalteparin or placebo.

plications and death. The results show significantly better ulcer outcome in patients treated with dalteparin compared with treatment with placebo. In the dalteparin group, more patients healed with intact skin and decreased the ulcer area >50% compared with the placebo group. Dalteparin treatment also reduced the amputation rate to 25% ( $n = 2$ ) of that found in the placebo group ( $n = 8$ ).

Patient characteristics were similar in both groups except that more ex-smokers had been randomized to treatment with placebo. Smoking has been related to retarded wound healing (16) and to insulin resistance (17). However, in the present study, the number of current smokers did not differ between treatment groups, and because 5 years or more had elapsed since ex-smokers quit smoking, smoking history is unlikely to have confounded the treatment effect of dalteparin.

Glycemic control is of major importance for microvascular complications in diabetes (18,19) and is most likely also important for macrovascular complications (19). In the present study, the majority of patients were treated with insulin, whereas a small number of patients had treatment with tablets and/or diet only. Metabolic control, as measured by HbA<sub>1c</sub>, was remarkably good in both treatment groups throughout the study.

All patients included in the present study had neuro-ischemic foot ulcers. Time to healing with intact skin during the observation time of 6 months was similar in the dalteparin and placebo groups, probably because patients were followed up during a certain period of time and not to final outcome. Patients

with neuro-ischemic foot ulcers are generally older, have larger foot ulcers, and have longer healing times than patients with pure neuropathic foot ulcers (20). The site of foot ulcers is important and related to ulcer healing (21), with the lowest healing and highest amputation rates reported in patients with multiple foot ulcers, i.e., three or more ulcers (21,22). In the present study, the number of patients with multiple ulcers was similar in the dalteparin and the placebo group. In contrast, three of the patients with multiple ulcers on placebo went to amputation compared with none in the dalteparin group. On the other hand, more patients with toe ulcers had been randomized to placebo treatment, which might have contributed to the higher frequency of minor amputations in this group.

The mechanisms behind the beneficial effect of dalteparin on outcome of neuro-ischemic foot ulcers in patients with diabetes are unclear, but several factors are most likely involved. Earlier studies by our group have demonstrated a severely impaired skin capillary circulation in the feet of diabetic patients with PAOD (5), to which hemorheological disturbances related to a high plasma fibrinogen concentration might contribute. LMWH and unfractionated heparin are potent antithrombotic agents that also enhance the fibrinolytic activity and have anti-inflammatory effects (23–26). LMWH also stimulates angiogenesis and improves the arterial circulation, e.g., the coronary circulation (27,28). Heparin normalizes the proliferation of diabetic chronic wound fibroblasts (29), and Kratz et al. (30) showed a positive effect of

topical application of heparin on wound healing in skin graft donors. Infection and ischemia are two important factors contributing to impaired ulcer healing in diabetic patients. Accordingly, the seven patients who deteriorated on treatment with dalteparin had higher serum hsCRP concentration and lower TBP than the corresponding patients on placebo. Otherwise, serum concentrations of the acute phase reactants hsCRP and S-AA were similar in the two treatment groups, both at baseline and at study termination, indicating a similar degree of inflammation and/or infection in the two treatment groups.

In conclusion, the present study shows for the first time that treatment with dalteparin improves the ulcer outcome in diabetic patients with PAOD and chronic foot ulcers. However, it would be of major interest to confirm the current results in a larger trial. Chronic foot ulcers cause a lot of suffering for the patients and are one of the most expensive diabetic complications for society—especially healing after amputation (1). The positive effects of dalteparin on ulcer healing might greatly affect the costs and care of diabetes.

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