Eur J Vasc Endovasc Surg **29**, 190–198 (2005)
doi:10.1016/j.ejvs.2004.11.011, available online at http://www.sciencedirect.com on SCIENCE DIRECT®

Effects of Three Months of Low Molecular Weight Heparin (dalteparin) Treatment After Bypass Surgery for Lower Limb Ischemia—A Randomised Placebo-controlled Double Blind Multicentre Trial

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Objectives. *To test the hypothesis that long-term postoperative dalteparin (Fragmin®, Pharmacia Corp) treatment improves primary patency of peripheral arterial bypass grafts (PABG) in lower limb ischemia patients on acetylsalicylic acid (ASA) treatment.*
Design. *Prospective randomised double blind multicenter study.*
Materials and methods. *Using a computer algorithm 284 patients with lower limb ischemia, most with pre-operative ischemic ulceration or partial gangrene, from 12 hospitals were randomised, after PABG, to 5000 IU dalteparin or placebo injections once daily for 3 months. All patients received 75 mg of ASA daily for 12 months. Graft patency was assessed at 1, 3 and 12 months.*
Results. *At 1 year, 42 patients had died or were lost to follow-up. Compliance with the injection schedule was 80%. Primary patency rate, in the dalteparin versus the control group, respectively, was 83 versus 80% (n.s.) at 3 months and 59% for both groups at 12 months. Major complication rates and cardiovascular morbidity were not different between the two groups.*
Conclusions. *In patients on ASA treatment, long-term postoperative dalteparin treatment did not improve patency after peripheral artery bypass grafting. Therefore, low molecular weight heparin treatment cannot be recommended for routine use after bypass surgery for critical lower limb ischemia.*

Keywords: Limb ischemia; Bypass; Graft; Patency; Low molecular weight heparin.

Introduction

Critical limb ischemia (CLI) is usually caused by peripheral atherosclerotic disease (PAD) mainly below the renal arteries.[1] In the long run a majority of CLI patients, if untreated, will develop ischemic ulcerations and gangrene provided the patient survives long enough.[1] Most patients with CLI can be successfully treated, at least in the short-term, by peripheral arterial surgery or endovascular procedures.[2] In Sweden, the majority of such patients with symptoms due to PAD below the inguinal ligament will have a peripheral arterial bypass graft (PABG) rather than an endovascular procedure (Swedvasc 2003, unpublished observation). Although patency rates of PABG at 30 days often is reported to be in the range of 95%, many series report that within a year 30–40% of such grafts will be occluded.[3] Graft occlusions usually result from progression of the underlying PAD, and/or by intimal hyperplasia (IH) either in graft-artery anastomoses, or in the body of vein grafts.[4] These lesions are believed to involve proliferation of smooth muscle cells (SMC) in the arterial wall in response to vascular injury.[5] Heparin inhibits SMC proliferation after experimental

Presented at the ESVS meeting in Istanbul 2002.
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1078–5884/000190 + 09 $35.00/0

arterial injury.[6] Also low molecular weight heparins (LMWH) have been reported to inhibit SMC proliferation in the experimental situation, and LMWH are known to give a more predictable anticoagulation response than heparin.[7,8] Furthermore, the clinical usefulness of LMWH is greater than for heparin due to better bioavailability, the possibility of once daily administration and the effect of LMWH to lower plasma viscosity.[9]

A large number of studies have reported the safety and efficacy of LMWH for prevention of deep vein thrombosis (DVT) after surgery and for treatment of DVT in outpatient settings.[10,11] More recent data suggest that LMWH also may have a role in other vascular beds, e.g. the coronary arteries.[12] Despite the use of LMWH for DVT prophylaxis/treatment and in acute coronary syndromes, their possible role in vascular surgery remains unclear. Edmondson and coworkers studied patency at 1 year in 201 patients undergoing femoropopliteal bypass due to CLI or intermittent claudication and treated with long-term LMWH (dalteparin) or acetylsalicylic acid (ASA) and dipyridamole.[13] Subgroup analysis of the 93 CLI patients in their randomised but unblinded study showed much higher patency at 1 year in the dalteparin than in the control group (90 versus 48%). The implications of this study are not clear.[14] If such findings are reproducible, the widespread use of long-term LMWH treatment after peripheral artery bypass grafting (PABG) for CLI would be warranted.

In the present randomised double blind study we investigated the effects of long-term treatment with LMWH (dalteparin) injections in patients undergoing PABG for lower limb ischemia in a large placebo-controlled study in patients treated with low-dose ASA.

Methods

Setting

This multicentre, randomised, double blind trial was conducted in 12 vascular surgical centres in western Sweden and Stockholm. The study was conducted according to the Guidelines for Good Clinical Practice for research and the Declaration of Helsinki. It was approved by the Ethical Committee of the Sahlgrenska Universitetssjukhuset for the western Sweden area, and in the Karolinska Institute for the Stockholm Hospitals.

Objectives

The primary objective was to evaluate the primary graft patency (patent graft without any further ipsilateral arterial intervention) 3 and 12 months after PABG surgery in patients receiving 3 months of treatment with the study drug, subcutaneous injection of dalteparin (Fragmin®), as compared to placebo injections. Patients were included after having undergone bypass surgery for lower limb ischemia, e.g. axillofemoral, femorofemoral, femoropopliteal, femorocrural, femoropedal, axillopopliteal, iliacopopliteal, popliteopedal, popliteopopliteal, tibiotibial, and similar bypass operations, or revisions thereof within 3 days from the primary bypass procedure (full inclusion criteria are listed in Table 1). Upon inclusion, before the PABG, the investigator gave information about the study and received a signed informed consent from the patient. Patients undergoing aortoiliac or aortofemoral bypass were excluded (Table 1).

Secondary objectives were to evaluate:

1. healing of ischemic foot ulcerations, and the degree of ischemic rest pain in the operated leg,
2. patient acceptability of self injections as treatment after PABG for lower limb ischemia,
3. graft patency, and incidence of failing graft at 3 and 12 months in patients with a patent graft at 1 month, and at 4–7 days after the operation, respectively,
4. incidence within 12 months of bypass of myocardial infarction, transient ischemic attacks (TIA), unstable angina, minor and major stroke, gangrene, re-operations (including endovascular procedures), amputation of the ipsilateral or contralateral leg and other bypass procedures,
5. deaths within 12 months.

Included in the third secondary objective was a comparison of the two groups with respect to the time to the first event/and the number of events of graft occlusion, revision for failing graft, and reoperations including endovascular procedures.

Study design

The study was multicentre, placebo controlled, randomised, double blind with parallel groups. After PABG surgery, but before randomisation, patients once daily received 5000 IU of subcutaneous dalteparin. All patients underwent assessment of medical history including concomitant medication and smoking status. The physical examination included assessment of the degree of ipsilateral ischemic pain,

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Lower limb ischemia due to PAD, w/wo diabetes, and with symptoms being present for more than 2 weeks	Patient needing permanent oral anticoagulant treatment
With current symptoms including one or more of the symptoms rest pain, ischemic ulceration, partial gangrene	Known allergy and/or definite contraindication to acetylsalicylic acid, and/or LMWH
Operated with a PABG for lower limb ischemia	Previous treatment under this protocol
w/wo a revision procedure within 1–3 days of a PABG#, but before start of study treatment, and	Woman of childbearing potential unless taking adequate contraception
Proven patency of the graft within <1 h before randomisation	Patient participating in another clinical pharmaceutical study, where another drug is under investigation
Adult of either sex, >39 years old	Surgery with a known risk of increased bleeding postoperatively, as judged by the investigator, e.g. involving the eye, ear or central nervous system, within 3 months
Expected to survive >1 year, and	Hemorrhagic stroke within 6 months
Giving written informed consent	Hemorrhagic diathesis, e.g. thrombocyto-penia (<100×109/l) or hemophilia
	Prothrombin time (PT) <50% due to hepatic disease
	Renal failure (serum creatinine >260 μmol/L)
	>2 revisions of the PABG after the primary operation and before randomisation

#, peripheral arterial bypass graft

ischemic ulcerations and gangrene, and bilateral ankle pressure (AP) measurements. A 12 lead ECG and laboratory tests including haemoglobin, leukocyte and platelet count, s-ASAT and s-ALAT, serum electrolyte status including serum creatinine and prothrombin level were taken.

Study drug treatment was started after the randomisation, which took place 2–4 (if there was a holiday during the weekdays, a minimum of one and a maximum of 5 days were allowed) days after the bypass procedure, depending on which weekday the patient underwent the operation. Randomisation was performed 2 days after surgery for patients operated upon from Monday until Wednesday, after 4 days for those operated upon on a Thursday and after 3 days for those operated upon on a Friday.

The treatment group received dalteparin 5000 IU by a subcutaneous injection of 0.2 mL once daily for 3 months. The control group received subcutaneous 0.2 mL placebo injection once daily for 3 months. All patients were given 75 mg of ASA (Trombyl®) orally once daily for the 12 months follow-up period starting no later than the same day as the first study injection.

Dalteparin sodium was supplied in pre-filled, single-dose syringes for subcutaneous injection, each containing 5000 anti-FXa IU/0.2 mL. Placebo syringes contained 0,2 ml 0,9% sodium chloride and looked identical to those containing the study medication. The blinding procedure was ensured since the study drug and placebo syringes were identical in appearance and since neither the investigator/study team, nor the patient or the monitor were before the study was finished aware of which treatment the patient received.

Each patient received one box containing 40 syringes with study medication A or B by the time of randomisation. While the patient remained in the hospital, the investigator stored the patient's study drug. After discharge from the hospital the study medication was stored in the patient's home. Approximately 30 days after randomisation, at the first follow-up visit, the patient received two new boxes with the study medication, altogether containing 70 syringes.

Drug compliance during the first three study months was assessed in a patient diary. The diary contained data for the amount of administered injections and the intake of ASA over a 3 months period. The patient returned unused syringes to the local pharmacy, where the unused syringes were counted. After the third study month, the patient's intake of ASA for the remaining 9 months of the study was reported by the patient and evaluated in connection with the follow-up visits. Good compliance for the injections during the first 15 days was defined as at least 12 out of 15 injections taken, and for the last 75 days at least 65 out of 75 injections taken, and not missing injections for more than three consecutive days. Good compliance for ASA was defined as the patient regularly taking ASA, as reported in the patient diary.

Randomisation

In order to ensure a correct balance between the two groups, patients were randomised using a computer algorithm method, taking into account 17 different parameters believed to be of potential relevance for the patency of PABG. Data included in the randomisation

Table 2. Data included in the computer algorithm

Hospital	Weekday for operation
Age	Sex
Smoking last week	Diabetes
Malignant disease	Detsky cardiac risk index*
Preoperative ischemic rest pain (none, moderate, severe)	Preoperative ischemic ulceration (none, one <3 cm, one >3 cm or several)
Preoperative gangrene (no, yes)	Ankle pressure (mmHg)
Bypass procedure	Graft material (e.g. vein, PTFE)
Revision of bypass performed before randomisation	No of fully patent crural arteries (from zero to three)
Surgeon's estimation of the risk for graft occlusion within 12 months (low, medium, high)	

* Ref. [15].

procedure are shown in Table 2. The surgeon estimated the risk for graft occlusion within 12 months as low, medium or high based on his/her own opinion, after having performed PABG, taking into account all available information including intra-operative findings.

Randomisation was performed by one of two registered nurses at the Vascular Laboratory in the Sahlgrenska University Hospital's Vascular Surgery Unit. Each centre submitted a fax to the randomisation centre, including the clinical data, and within 60 min a reply fax was sent to the study site stating the patient number and the clinical trial number for the patient. Simultaneously, a second fax was sent to the hospital pharmacy at the study site giving all details of the patient and information on whether the patient should receive treatment A or B. These faxes were not available to the patient, monitor, investigator or study team at any of the study sites. At the end of the study when the code was broken, the signed randomisation papers, which had been faxed to each study centre, and the local pharmacy treatment list were collected by the monitor together with the checklist. The treatment code was not broken until clean file was declared and the statistical analysis had been performed, i.e. when all data had been entered, checked, and the data-base was protected against changes.

Criteria for patency and assessment of ulcerations and gangrene

Patency was assessed by standard clinical means, including the use of a handheld Doppler, although duplex examination was used routinely in some centres. At 12 months a duplex examination of the graft, or angiography, was mandatory to establish graft patency.

A graft was considered patent if at least one of the following criteria were met:

1. Arterial pulsation palpable in one or more arteries distal to the graft.
2. Pulses palpable in the graft and arterial blood flow (Doppler) present in the graft. Not valid for *in situ* bypass.
3. Arterial blood flow (Doppler) demonstrated in the graft and post-operative ABI > 0.15 higher than pre-operative ABI.
4. Distal blood flow (Doppler signal) that disappears or decreases significantly upon proximal compression of the graft, or ischemic pain and ulcerations completely relieved.
5. Postoperative ABI > 0.20, and/or toe pressure > 20 mmHg higher than preoperatively.
6. Flow demonstrated by color Doppler/duplex and/or arteriography.
7. Intra-operative findings, i.e. revision/amputation, or suggested by an autopsy. Not valid for follow up visits, but for patients withdrawn, lost to follow-up or dead.
8. Good skin color and better warmness of the foot, compared to pre-operatively and compared to contralateral foot. This criterion was used on postoperative days 1–7 only.

If patency during follow-up was not clearly documented at least by one of 1–5 above and it was not clear whether the graft was occluded, a duplex and/or an arteriography and/or a surgical procedure was mandatory to define the patency status of the graft. Patency also was assessed if an amputation/revision involving the graft became necessary. The presence of graft occlusion was, whenever possible, studied in connection with autopsies in patients that died during the follow-up period.

Severity (improved, unchanged or worsened) of ischemic ulceration and partial gangrene was made subjectively, by the responsible surgeon, during the patient's visits at the outpatient clinic. Formal measurement of the size of ischemic ulcers and partial gangrene was not mandatory.

Hypothesis and determination of sample size

Graft patency, 1 year after PABG for severe limb ischemia, was estimated to be 60% in the placebo + ASA group, based on unpublished data from the Swedvasc. Based on the results in the study by Edmondson and coworkers,[13] we based sample size calculations on the hypothesis that the patency rate would be 78% in the dalteparin + ASA group. Due to the serious nature of concomitant diseases, we assumed that only 65–75% of the patients would have graft follow up at 1 year. With 75% of the patients having grafts evaluated at 1 year, with alpha = 0.05 and beta = 80% and using two-sided tests, 280 patients needed to be randomised. An interim analysis to assess safety was conducted after 160 patients had been randomised and indicated that over 80% patients survived to have grafts evaluated at 1 year.

Calculation of patency, and statistical methods

In the present study, patency was investigated at prespecified points of time (1, 3 and 12 months). In order to facilitate comparisons with studies where patency is spontaneously reported and presented by use of Kaplan–Meier curves the survival functions were calculated. The calculations were performed on the assumption that the hazard functions were piecewise constant, changing after 1 and 3 months. The probabilities of graft patency in the two treatment groups at 3 and 12 months, respectively, were compared by Fisher's exact test. The same test was also used for comparison of the acceptability of treatments. For the time to first occlusion or failing graft, the log rank test was applied. The latter test was applied for comparisons with respect to a set of secondary end-points, which were registered as events with a date. For other variables such as ischemic pain, healing of ischemic ulcers Fisher's permutation test was used.[16] In order to assess variables of importance for graft patency, besides treatment with dalteparin, logistic regression analyses were performed. The possible effect of the duration (1–5 days) of the initial postoperative dalteparin medication was assessed by introducing an interaction term in the logistic model between the duration of this initial treatment in patients randomised to placebo. Confidence intervals for the difference between the patency probabilities were calculated. All tests were two-sided.

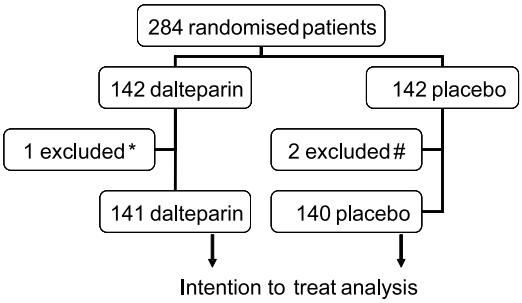

Fig. 1. Flow diagram of randomised patients. Explanations; *, one patient had occluded bypass graft by the time of randomisation and was, therefore, excluded (protocol violation); #, two patients did not continue in any form after randomisation and were, therefore, excluded.

Results

Altogether 284 patients (46% of all patients operated upon with the mentioned peripheral arterial bypass procedures for severe lower limb ischemia during the inclusion period in the participating centres) were randomised (Fig. 1). Two patients were withdrawn early after randomisation. One further patient with an occluded bypass by the time of randomisation also was excluded, leaving 281 patients for final analysis: 141 in the dalteparin and 140 in the control group.

All demographic and basal clinical data for the included patients were similar in the two groups (Table 3). The risk for occlusion of the bypass as estimated by the vascular surgeon after the PABG operation was judged as low, average and high in 26, 86 and 29 dalteparin patients, respectively. The corresponding numbers in the placebo group were 26, 85 and 29, respectively. Thirty-two patients died during the 12 months follow-up period.

Compliance for the study injections was not different between the two groups during early

Table 3. Clinical data at randomisation

Variable	Dalteparin (n = 141)	Placebo (n = 140)
Reoperation before randomisation	7% (11)	6% (8)
Female sex	45% (63)	45% (63)
Present smoker	31% (44)	30% (42)
Malignancy	2% (3)	1% (2)
Ischemic ulcer	58% (82)	57% (80)
Partial gangrene	27% (38)	28% (39)
Diabetes	37% (52)	36% (50)
Age (SD)	73 (9)	74 (9)
Ankle pressure* (SD)	67 (56)	60 (37)
Detsky cardiac risk index (SD)[15]	1.1 (0.5)	1.1 (0.3)

The percentage of the presence of each variable is given, and the number of patients within parenthesis. There are no significant differences between the two groups.

* Includes all patients and values, also diabetics with high ankle pressures.

Table 4. Twelve months patency (primary, and primary assisted) for different types of bypass and graft materials

Type of PABG	Vein (V) or synthetic (S) graft	Occluded at 12 months	Patent at 12 months	Primary patency rate
Axillo- or femorofemoral	–	9	30	0.77
Fem-pop AK	S	11	22	0.67
Fem-pop AK	V	6	14	0.70
Fem-pop BK	S	14	18	0.56
Fem-pop BK	V	14	38	0.73
Fem-tib or -ped	S	6	7	0.54
Fem-tib or -ped	V	22	35	0.61

follow-up. For the first 14 days, 120/141 (85%) patients on dalteparin showed similar, good compliance as compared to 128/140 (91%) patients assigned to placebo. Compliance for the injections was lower in the dalteparin group during follow-up from day 15 and until 3 months. For this latter period 99/141 (70%) dalteparin and 115/140 (82%) placebo patients showed good compliance ($p=0.0269$, Fisher's exact test). Patency was unrelated to good compliance for both groups. Good compliance for the ASA treatment was observed for 107/141 (76%) dalteparin and 102/140 (73%) placebo patients.

Patency at 12 months was highest for proximal procedures (axillofemoral and femoro-femoral grafts) and, as expected, lowest for femorotibial and femoropedal procedures with synthetic graft (Table 4). Although primary patency was slightly higher in the dalteparin (83%) versus the control group (80%) at 3 months (Fig. 2), this difference was far from significant ($p=0.396$). At 12 months, patency was identical (59%) in the two groups. Early mortality was low, and the deaths in each group at 1, 3 and 12 months are given in Table 5.

Patients who had a patent (primary or primary assisted) PABG at 12 months were compared with those who did not (Table 5). Only the surgeon's estimation of the risk for occlusion, as registered after the PABG procedure, was significantly related to graft patency ($p=0.032$) (Table 6). Age and the Detsky cardiac risk index were close to significance ($0.05<p<0.10$). None of the other randomisation variables was related to graft patency at 12 months. Patency in the placebo group was not associated with the duration (1–5 days) of initial dalteparin treatment.

Change in ischemic ulceration and/or partial gangrene was not different between the two groups at either 3 or 12 months. In patients with diabetes 23/70 (77%) in the dalteparin and 25/32 (78%) in the placebo group showed improved status at 12 months. In patients without diabetes 29/45 (64%) dalteparin patients showed improved status as compared to 27/59 (46%) placebo group patients ($p=0.0893$).

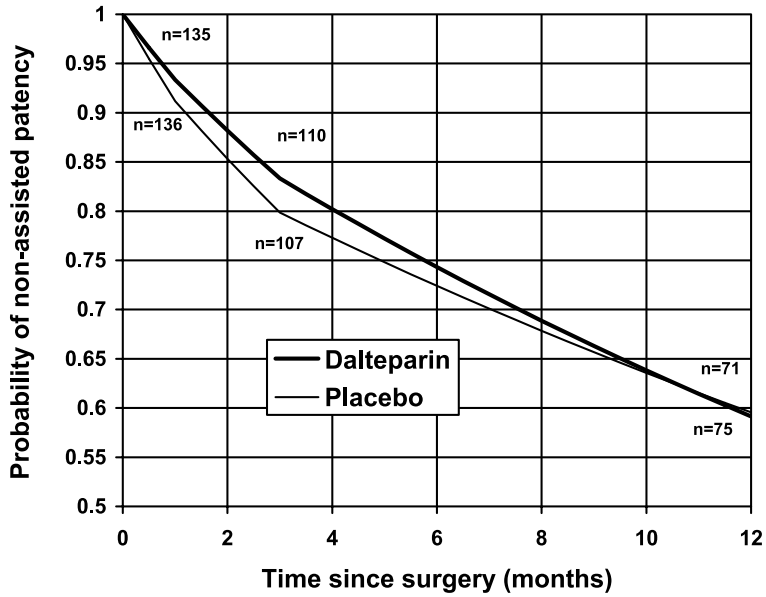

Fig. 2. Primary patency in the dalteparin and control groups during follow up. There was no significant difference between the two groups.

Table 5. The number of patients in the different categories at 3 and 12 months

	Dalteparin at 3 months	Placebo at 3 months	Dalteparin at 12 months	Placebo at 12 months
Primary patency	110	107	71	75
Primary assisted patency	4	2	11	7
Not patent*	14	21	26	30
Ipsilateral amputation	3	3	7	9
Dead	5	3	17	15
Missing value	5	4	9	4

* Alive and without ipsilateral amputation.

The amount of gangrene at 12 months, assessed as none, less than forefoot or more than forefoot, was not different between the two groups. In the dalteparin group, 32/34 (94%) patients with diabetes and 65/67 (97%) patients without diabetes had no gangrenous tissue at 12 months. The corresponding figures in the placebo group were 31/34 (91%) and 71/72 (99%) patients, respectively. Similarly there were no differences in the number of patients with ischemic ulceration at 12 months. In the dalteparin group 28/35 (80%) with diabetes and 56/67 (84%) without diabetes had no ischemic ulceration at 12 months. The corresponding figures in the placebo group were 27/34 (79%) with diabetes and 70/73 (96%) of those without diabetes.

Adverse events were common in both groups, but there was no difference between the two groups (Table 7). Overall, there were 20 bleeding complications in the dalteparin versus 17 in the placebo group. Most reported bleeding complications were not serious, and no treatment was needed.

Table 6. Basal clinical data in patients with primary or primary assisted patency, or not at 12 months

Variable	Patency or primary assisted patency at 12 months	
	Yes ($n=164$)	No ($n=82$)
Ankle pressure, mean (SD)	65.0 (48.7)	64.8 (49.8)
Age, mean (SD)	73.9 (8.1)	72.2 (9.4)
Smoker %	30	32
Malignancy %	1	2
Ischemic ulceration %	52	62
Detsky cardiac risk index, mean (SD)	1.07 (0.27)	1.17 (0.56)
Revision of bypass %	4	11
Highest risk for occlusion %*	14	26†
Sex % female	48	45
Diabetes %	34	34
Gangrene %	21	37

* The risk for occlusion denotes the surgeon's opinion, as recorded after PABG surgery, of the risk for occlusion of the bypass within 1 year.
† $p<0.05$.

Discussion

In this randomised double blind study after peripheral arterial bypass graft surgery in patients on 75 mg of ASA daily, we observed no difference in graft patency at 3 or 12 months between patients receiving 5000 IU of dalteparin daily for 3 months after bypass surgery versus those receiving placebo injections. Active treatment with dalteparin did not improve the incidence of failing graft, amputation or other cardiovascular complications during 12 months of follow-up. Similarly there was no difference in either the fate or extent of ischemic foot ulceration and/or gangrene during 12 months of follow-up. Furthermore, there was no difference, between the groups, in the extent of gangrene or ischemic ulceration at 12 months.

Early mortality was low and similar in the two groups. Mortality within 12 months was much lower than expected from a comparison with all patients undergoing similar operations in Sweden reported to the Swedish In-patient Registry. Our patients were selected for this study on the basis of an expected 12 months survival, assessed subjectively by the responsible surgeon. Therefore, patients with advanced

Table 7. Number of adverse events in the two groups

Adverse event	Dalteparin	Placebo	Significance
Myocardial infarction	8	11	Ns
Unstable angina	2	2	Ns
Minor stroke#	3	2	Ns
Major stroke#	4	1	Ns
Transient ischemic attack#	2	0	Ns
All cerebrovascular (#)	9	3	Ns ($p=0.1407$)
Gangrene	5	2	Ns
Reoperations (including EVP)	30	27	Ns
Ipsilateral amputation	13	17	Ns
Contralateral amputation	5	6	Ns
Other bypass surgery	13	6	Ns

#, all cerebrovascular events is the sum of minor and major strokes and transient ischemic attacks.

malignant disease were excluded, as were patients a recent stroke or with renal failure. All trial patients were given low dose ASA treatment, which is known to improve survival in patients having undergone vascular surgery.[17] Possibly not all patients undergoing PABG in Sweden are given ASA after the bypass surgery. All patients in the present study were followed closely at least three times during the postoperative 12 months, and follow-up visits included recent medical history and a comprehensive medical status. Therefore, the better survival observed in the trial population as compared to all similar patients in Sweden may be due both to selection of patients at lower risk and to better treatment and follow-up.

Previous studies of LMWH in peripheral vascular patients have suggested that LMWH is as safe and at least as effective as unfractionated heparin in the prevention of DVT after vascular surgical procedures.[18] In a retrospective study in which LMWH was compared to unfractionated heparin for postoperative anticoagulation after vascular surgery it was suggested that LMWH was safe and effective for postoperative anticoagulation and could reduce the average postoperative length of stay.[19] However, due to the retrospective nature of the study, the authors concluded that further data of prospective nature were needed before safe conclusions could be drawn regarding the efficacy and safety of postoperative anticoagulation with LMWH.

The effect of LMWH, unfractionated heparin and dextran 40 on early graft patency has been studied previously. A randomised trial showed that patency, 3 months after femorodistal bypass surgery, was not different between patients receiving the LMWH enoxaparin and patients receiving dextran during the peri-operative period.[20] Patency at 3 months was of the same order of magnitude as that observed in the present study. In another open randomised multi-centre study of 201 patients undergoing femoro-distal bypass surgery patients were treated with subcutaneous LMWH or unfractionated heparin twice daily for 10 days.[21] The primary endpoint was graft patency on day 10 after surgery, as assessed clinically and/or by arteriography during reintervention and/or autopsy. Graft occlusion was more common in the unfractionated heparin group (22 versus 8%, $p=$ 0.009). Safety was not different and no differences were detected in other major complications. In a randomised study published in 1998, dextran 40 did not increase early (30 days) patency after autogenous infrainguinal bypass.[22]

A review published in 1999 of published clinical trials of adjuvant medical therapy in conjunction with infrainguinal bypass procedures demonstrated that only ASA in prosthetic grafts and ticlopidine in vein grafts have been shown to improve patency.[23] In the ticlopidine study there was no significant difference between ticlopidine and placebo regarding overall mortality or major ischemic events.[24] A large meta-analysis of randomised trials demonstrated that antiplatelet therapy reduced by 23% serious vascular events (death, myocardial infarction and stroke) among patients having undergone peripheral bypass grafting.[17] Comment was made in another review published in 1999 that the evidence for antiplatelet therapy and oral anticoagulants reducing the risk of graft occlusion effects is based on a small number of trials only.[25] In the Dutch Bypass Oral Anticoagulants or Aspirine Study published by the same authors a year later, oral anticoagulation was shown to be superior for prevention of infrainguinal vein graft occlusion and for lowering the rate of ischemic events, with optimum anticoagulation with an INR in between 3.0 and 4.0.[26,27]In contrast, ASA appeared better for the prevention of prosthetic graft occlusion, and was associated with fewer bleeding episodes.[26]

In a recent study, the ischemia induced by femoropopliteal bypass graft occlusion was observed to be worse with PTFE than with vein grafts, and the combined treatment with oral anticoagulants and aspirin was found to lessen the severity of the acute ischemia after occlusion of PTFE grafts as compared with aspirin treatment alone.[28] Such an effect was not observed in femoropopliteal vein grafts, and occlusion of such grafts was rarely accompanied by severe ischemia.

We based our hypothesis for a beneficial effect of dalteparin on the observations of Edmondson and coworkers,[13] but our study differs markedly. We undertook a double blind trial and did not include patients with intermittent claudication. In the Edmonson study, the techniques/criteria used to define graft patency was not described, both patients and investigators were aware of the treatment allocation and only the control group received ASA treatment (in addition to dipyridamole). Our study design permits more robust conclusions to be drawn.

In summary, the results of this study do not support the hypothesis that, in patients with severe lower limb ischemia, the patency of peripheral arterial bypass grafts is improved by the use of long-term postoperative LMWH treatment. Therefore, we believe routine long-term LMWH treatment after peripheral arterial bypass graft surgery for lower limb ischemia is not justified.

Acknowledgements

This work was supported by The Swedish National Heart and Lung Foundation, Nils Gunnarssons legat, Tore Nilssons Foundation, The LUA project of Göteborg University, and by Pharmacia Corporation, Sweden. The corresponding author had a consulting agreement with Pharmacia Corporation, Sweden.

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Accepted 17 November 2004