CLINICAL STUDIES

INTERVENTIONAL CARDIOLOGY

Low Molecular Weight Heparin (Reviparin) in Percutaneous Transluminal Coronary Angioplasty

Results of a Randomized, Double-Blind, Unfractionated Heparin and Placebo-Controlled, Multicenter Trial (REDUCE Trial)

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Objectives. The specific objective of the REDUCE trial was to evaluate the effect of low molecular weight heparin on the incidence and occurrence of restenosis in patients undergoing percutaneous transluminal coronary angioplasty (PTCA).

Background. Unfractionated heparin and its low molecular weight fragments possess antiproliferative effects and have been shown to reduce neointimal smooth muscle cell migration and proliferation in response to vascular injury in experimental studies.

Methods. The REDUCE trial is an international prospective, randomized, double-blind, multicenter study. Twenty-six centers in Europe and Canada enrolled 625 patients with single-lesion coronary artery obstructions suitable for PTCA. Three hundred six patients received reviparin as a 7,000-U bolus before PTCA, followed by 10,500 U as an infusion over 24 h and then twice-daily 3,500-U subcutaneous application for 28 days. The 306 patients in the control group received a bolus of 10,000 U of unfractionated heparin followed by an infusion of 24,000 U over 24 h. These patients then underwent 28 days of subcutaneous placebo injections. The primary end points were efficacy (defined as a reduction

in the incidence of major adverse events [i.e., death, myocardial infarction, need for reintervention or bypass surgery]), absolute loss of minimal lumen diameter and incidence of restenosis during the observation period of 30 weeks after PTCA.

Results. Using the intention to treat analysis for all patients, 102 (33.3%) in the reviparin group and 98 (32%) in the control group have reached a primary clinical end point (relative risk [RR] 1.04, 95% confidence interval [CI] 0.83 to 1.31, p = 0.707). Likewise, no difference in late loss of minimal lumen diameter was evident for both groups. Acute events within 24 h occurred in 12 patients (3.9%) in the reviparin group and 25 (8.2%) in the control group (RR 0.49, 95% CI 0.26 to 0.92, p = 0.027) during or immediately after the initial procedure. In the control group, eight major bleeding complications occurred, and in the reviparin group, seven were observed within 35 days after PTCA.

Conclusions. Reviparin use during and after coronary angioplasty did not reduce the occurrence of major clinical events or the incidence of angiographic restenosis over 30 weeks.

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Since the introduction of percutaneous transluminal coronary angioplasty (PTCA) in 1977 (1), this method has shown impressive clinical results in the acute setting. Increased experience and rapid advances in technology have resulted in a primary success rate of up to 95%. However, late restenosis, which constitutes the most important problem after successful angioplasty, continues to occur in 30% to 50% of patients within 3 to 6 months (2–5). Experimental and human postmortem studies have shown (6,7) that the process of restenosis is at least in part due to neointimal proliferation. Although the incidence, timing, clinical, anatomic and pathophysiologic factors associated with restenosis have been studied in depth (8–14), most medical attempts to reduce the occurrence of restenosis thus far have failed.

Unfractionated heparin has long been known as an effective anticoagulant with inhibitory action on platelet function and an additional effect on smooth muscle cell proliferation. In recent years, low molecular weight heparins have been developed and

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Abbreviations and Acronyms

CI   = confidence interval
NHLBI   = National Heart, Lung, and Blood Institute
PTCA   = percutaneous transluminal coronary angioplasty
RR   = relative risk
TIMI   = Thrombolysis in Myocardial Infarction

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have been shown to be as effective and safer than unfractionated heparin in the prevention and treatment of venous thromboembolism (15,16). Reviparin is a new low molecular weight heparin with anticoagulatory efficacy comparable to unfractionated heparin and a better safety profile than unfractionated heparin (17,18). In vitro studies with reviparin have shown significant inhibition of smooth muscle cell migration and proliferation in human cell cultures without affecting endothelial cell growth (19). Experimental studies in New Zealand rabbits (20) revealed that the extent of intimal mitosis during the first 7 days after PTCA was significantly reduced ($p < 0.01$ at 3 days; $p < 0.05$ at 7 days) after injections of reviparin (2.5 mg/kg body weight per day subcutaneously, which corresponds to 400 anti-Xa U/kg per day), resulting in only a moderate increase in intimal wall thickness after 28 days compared with that in a control group treated with unfractionated heparin. In a preliminary open clinical pilot trial conducted to evaluate the safety of reviparin application in the clinical setting, no increased bleeding complications were observed (21).

The purpose of the randomized, double blind, placebo-controlled, multicenter REDUCE trial (Reduction of Restenosis After PTCA, Early Administration of Reviparin in a Double-Blind, Unfractionated Heparin and Placebo-Controlled Evaluation) was to evaluate whether reviparin given intraarterially and intravenously during PTCA and subsequently subcutaneously twice daily for 28 days after PTCA in a dosage equivalent to that used in the animal experiments (20) and compared with unfractionated heparin and placebo would reduce the incidence of restenosis, as determined by the occurrence of major clinical events and angiography.

Methods

Selection of patients. Patients scheduled to undergo single-lesion coronary angioplasty (PTCA) because of stable or unstable angina (except for class 3C as defined in the Braunwald classification) were eligible for the study if they had no history of bleeding disorders, recent active bleeding, uncontrolled asthma or hypertension (blood pressure >180/105 mm Hg), active peptic ulcer disease, history of heparin-associated thrombocytopenia, acute myocardial infarction within 14 days and unstable angina requiring continuous heparin therapy. Patients had to have been suitable candidates for coronary bypass surgery. A left main coronary artery stenosis >50%, angioplasty of saphenous vein graft or previous PTCA at the

same lesion site also were exclusion criteria. The study was carried out according to the principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practice based on a study protocol. Written informed consent according to local practice was obtained for every patient.

Randomization. Patients were randomly assigned to either reviparin or unfractionated heparin plus placebo treatment. The randomization was realized at the centers by blinded, prepacked medication sets with ascending numbers. To ensure an equal distribution of treatments in each center, a block randomization procedure on a site basis in blocks of 12 treatment assignments was used. Patients were screened between May 1993 and June 1994. Six hundred twenty-five patients were enrolled at 22 European and 4 Canadian centers (see Appendix).

Study protocol. Standard balloon angioplasty was performed through the transfemoral approach using an 8F guide catheter according to standard techniques. At the time of arterial access, either a bolus of unfractionated heparin (10,000 IU) or reviparin (7,000 IU anti-Xa U) was injected into the femoral sheath. Subsequently, all patients received an intravenous infusion of either unfractionated heparin (24,000 IU) or reviparin (10,500 IU anti-Xa U) over 16 ± 4 h (mean ± SD). Aspirin (100 mg/day) was administered 1 day before and throughout the treatment period. Beginning on the evening of day 1, either 3,500 IU anti-Xa U of reviparin or placebo was administered subcutaneously twice daily for 28 days.

The clinical follow-up visit was scheduled 4 and 30 weeks after angioplasty for clinical and laboratory assessment. Laboratory assessment included complete blood count, coagulation profile and liver function tests. The global clotting tests (activated prothrombin time, thromboplastin time and anti-Xa plasma level) were analyzed at core laboratory (Sainte Marie, Paris, France for the European centers; McMaster University Medical Center, Hamilton, Ontario for the Canadian centers). Patient compliance with regard to subcutaneous injections was assessed by a patient booklet to be filled out and the measured anticoagulation levels after 28 days. To assess angiographic restenosis, repeat coronary angiography was performed at 26 ± 2 weeks after PTCA through the femoral sheath with a 7F femoral diagnostic catheter after readjustment of the X-ray gantry angular settings and the various height levels, according to values previously documented during the original intervention.

The angiograms were sent to the core angiographic laboratory for further blinded analysis. To standardize the method of data acquisition and to ensure the exact reproducibility of the angiograms acquired after intervention and follow-up, measurements were made using the Coronary Artery Analysis System, as described elsewhere (22). Ten percent of the angiograms were reanalyzed in blinded manner as part of the quality control assessment.

Study end points. The *primary clinical end point* was defined as the first occurrence of any of the following events in the first 30 weeks after the initial procedure: death from any cause; nonfatal myocardial infarction; clinically driven repeat

revascularization of the initial treatment vessel, including interventions using an alternative percutaneous revascularization device, coronary artery bypass surgery or implantation of a coronary stent as a bailout procedure. *Rescue stent implantation* was defined as the placement of a stent in the event of flow reduction to Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1. All emergency stent implantations were checked for the eligibility of the rescue criterion by the central angiographic committee.

Myocardial infarction was defined as documented elevation of serum creatine kinase levels to greater than twice the upper limit of normal for the laboratory; electrocardiographic changes indicative of myocardial infarction; or typical anginal pain at rest prolonged for >30 min despite administration of nitroglycerin.

The *primary angiographic end point* was defined in terms of absolute loss in minimal lumen diameter at the dilated site from after PTCA to follow-up angiography (median follow-up of 184 days after PTCA) assessed by quantitative coronary analysis. *Restenosis* was defined as loss of >50% of the initial gain of PTCA, according to the National Heart, Lung, and Blood Institute (NHLBI) 4 definition.

The safety of the trial medication and the feasibility of replacing standard heparin during the intervention was assessed in terms of occurrence of bleeding complications or other adverse events that could be attributed to the trial medication. In addition, bleeding was quantified as major or minor. *Major bleeding* was defined as a clinically evident bleeding episode associated with a decrease in hemoglobin of at least 2 g/dl or requiring transfusion of at least 2 U of blood, or both. Any intracerebral or retroperitoneal bleeding was considered a major episode. The site and source of bleeding episodes were noted.

Data management and statistical analysis. The primary variable for biometric clinical evaluation was the incidence of clinical events, as previously already defined. On the basis of data from previous trials (23), this trial was planned to include a minimum of 281 patients/group to detect a reduction of 40% in the primary clinical end point (the event rate in the control group was predicted to be 30%, with alpha = 0.05, beta = 0.1 [two-tailed Fisher exact test]). All data were monitored by the Data and Statistical Coordinating Center (clinical data) or the core laboratory (angiographic data) as well as the monitoring team of the trial sponsors. The Data and Statistical Coordinating Center performed the final statistical analysis.

The results of the two treatment groups were displayed as Kaplan-Meier survival curves (24). For the primary end point, a Mantel-Haenszel test was performed using the end point rates in the two treatment groups until the end of week 30. This analysis involved all randomized patients with the exception of 13 patients who did not receive study medication, according to the intention to treat principle. The primary angiographic end point was statistically evaluated by comparison between the two treatment groups with respect to loss of minimal lumen diameter from after PTCA to the 26 week follow-up visit and was performed according to the intention to treat principle for

Table 1. Baseline Clinical Characteristics of Intention to Treat Cohort

	UFH Placebo (n = 306) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]
Male	258 (84.3)	258 (84.3)	516 (84.3)
Mean (±SD) age (yr)	57.9 ± 9.4	58.4 ± 9.5	58.2 ± 9.5
Risk factors			
Diabetes mellitus	37 (12.1)	32 (10.5)	69 (11.3)
Hypertension	103 (33.7)	103 (33.7)	206 (33.7)
Hypercholesterolemia	149 (48.7)	150 (49.0)	299 (48.9)
History of smoking*	204 (66.7)	219 (71.6)	423 (69.1)
Previous MI	132 (43.1)	132 (43.1)	264 (43.1)
Angina class (CCS)			
None	17 (5.6)	18 (5.9)	35 (5.7)
I	50 (16.3)	44 (14.4)	94 (15.4)
II	109 (35.6)	124 (40.5)	233 (38.1)
III	68 (22.2)	62 (20.3)	130 (21.2)
IV	57 (18.6)	55 (18.0)	112 (18.3)
Missing	5 (1.6)	3 (1.0)	8 (1.3)

*History and current smokers. CCS = Canadian Cardiovascular Society; MI = myocardial infarction; UFH = unfractionated heparin.

514 patients for whom all three angiograms were available. Continuous variables are expressed as mean value ±SD and were compared in the treatment groups using covariance techniques with center and baseline values as covariates. The Mantel-Haenszel test stratified for centers was used to compare proportions. Discrete variables are expressed as counts and percentages as well as relative risk with 95% confidence interval, with respect to treatment groups. Comparisons among treatment groups with respect to all other variables excluding the primary clinical end point were made for descriptive purposes. Data are presented with nominal two-tailed p values (unadjusted for multiple comparisons).

Results

The intention to treat patient group included all patients who received at least one dose of the study medication. The clinical "per protocol" patient group included all compliant patients of the intention to treat clinical cohort who had an initial single-vessel single-lesion PTCA and a complete clinical follow-up. Three hundred six patients were randomized to receive unfractionated heparin/placebo and 306 to receive reviparin. Clinical or telephone follow-up for evaluation of the primary clinical end point was obtained for 601 patients. During the course of the study, eight patients were lost to follow-up, and three had their second follow-up visit before the end of week 30, and no telephone evaluation of the end point was obtained. The baseline characteristics of the intention to treat cohort are given in Tables 1 and 2. The two treatment groups did not differ in any baseline clinical or angiographic characteristics. In general, patients had one-vessel disease, and a single lesion was dilated in all patients according to the inclusion criteria. Comparison of baseline characteristics in the per protocol patient group also showed no difference in any

Table 2. Baseline Angiographic Characteristics of Intention to Treat Cohort

	UFH Placebo [no. (%)]	Reviparin [no. (%)]	Total [no. (%)]
No. of diseased vessels			
1	188 (76.1)	207 (77.5)	395 (76.8)
2	50 (20.2)	48 (18.0)	98 (19.1)
3	9 (3.6)	11 (4.1)	20 (3.9)
Unknown	0 (0.0)	1 (0.4)	1 (0.2)
% stenosis (QCA)*	66.2 ± 13.8	66.1 ± 13.1	66.1 ± 13.5
ACC/AHA lesion class			
A	35 (14.2)	41 (15.4)	76 (14.8)
B₁	115 (46.6)	133 (49.8)	248 (48.2)
B₂	92 (37.2)	89 (33.3)	181 (35.2)
C	5 (2.0)	4 (1.5)	9 (1.8)
Total	247	267	514

*Mean ± SD. ACC/AHA = American College of Cardiology/American Heart Association; QCA = quantitative coronary angiography; UFH = unfractionated heparin.

Table 3. Reasons for Exclusion From Per Protocol Cohort

	UFH Placebo (n = 306) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]
Lost to follow-up	8 (2.6)	3 (1.0)	11 (1.8)
Incorrect entry criteria*	14 (4.6)	5 (1.6)	19 (3.1)
Protocol violation	18 (5.9)	17 (5.6)	35 (5.7)
Other			
Follow-up too late	43 (14.1)	40 (13.1)	83 (13.6)
No balloon dilation performed	5 (1.6)	11 (3.6)	16 (2.6)
Consent withdrawn during study	5 (1.6)	3 (1.0)	8 (1.3)
Total exclusions	93 (30.4)	79 (25.8)	172 (28.1)

*Patients not meeting correct inclusion criteria at second review. UFH = unfractionated heparin.

baseline characteristic. Ninety-three patients in the control group and 79 in the reviparin group were excluded from the per protocol analysis. The primary reason for exclusion was insufficient compliance with the 6-month follow-up visit or missing protocol compliance. Nineteen patients did not meet entry criteria (Table 3). The mean dose of intravenous infusion was 92.16% for the control group and 93.05% for the reviparin group. Comparable compliance was observed for the administration of the subcutaneous injections.

Primary efficacy analysis. Using the intention to treat analysis (Table 4), treatment failure, as defined by the occurrence of death, myocardial infarction, bypass surgery and emergency or elective repeat PTCA in the observation period, was 33.3% for the reviparin group and 32% for the control group (relative risk [RR] 1.04, 95% confidence interval [CI] 0.83 to 1.31, p = 0.707) (Table 4). Angiographic restenosis using the NHLBI 4 definition was present in 86 (34.4%) patients in the control group and in 89 (33%) in the reviparin group. Only 61 (19.9%) patients in the control group and 50 (16.4%) in the reviparin group developed significant angina requiring repeat coronary angioplasty, indicating that a certain percentage of patients had aymptomatic restenosis. The occurrence of death and myocardial infarction was an infrequent event (2.6% in the control group [13 patients] and 4.5% [8 patients] in the reviparin group). Subsequent revascularization with bypass surgery or angioplasty was performed in 69 (22.6%) of the patients in the control group and in 82 (26.8%) of the patients in the reviparin group.

However, acute events during or immediately after the procedure (day 1) occurred in 12 (3.9%) patients in the reviparin group and in 25 (8.2%) of the control group (RR 0.49, 95% CI 0.26 to 0.92, p = 0.027) (Fig. 1). Emergency stent implantation in the acute stage was different in the two groups (21 patients in the control group vs. 6 in the reviparin group; RR 0.29, 95% CI 0.13 to 0.66, p = 0.003). Autoperfusion balloons in the event of TIMI perfusion grade 0 or 1 after angioplasty were used in 16 patients in the control group and

in 9 in the reviparin group (RR 0.519, 95% CI 0.24 to 1.12, p = 0.096). Nonfatal myocardial infarction occurred in three control group patients and four reviparin group patients subsequently after PTCA, and an emergency repeat PTCA was performed in one control group and two reviparin group patients. Analysis of primary end points after 30 weeks was additionally done for the per protocol clinical group. Major clinical events occurred in 64 patients (30%) in the control group and in 72 patients (31.7%) in the reviparin group (RR 1.03, 95% CI 0.78 to 1.36, p = 0.84).

Angiographic analysis. The change in minimal lumen and reference diameters before and after PTCA and at the 6-month follow-up visit were assessed for all patients in whom follow-up angiography was available (n = 514). The mean acute gain in minimal lumen diameter was 0.84 mm for the control group and 0.88 mm for the reviparin group. The mean late loss in minimal lumen diameter was 0.25 and 0.29 mm, respectively (p = 0.55, analysis of covariance). The cumulative distribution of the minimal lumen diameter before and immediately after PTCA and at follow-up angiography likewise showed no difference between the two groups and followed a gaussian distribution.

Bleeding complications. No substantial differences were found in the rate of major bleeding complications: 8 patients (2.6%) in the control group vs. 7 patients (2.3%) in the reviparin group (RR 0.88, 95% CI 0.32 to 2.41, p = 0.8). All major bleeding episodes occurred within 35 days after PTCA. There was one episode of intracerebral and one of intraocular bleeding in the reviparin group, and all except three major bleeding episodes in the control group occurred at the femoral arterial entry sheath (Table 5).

Discussion

The results of the present study demonstrate that reviparin did not reduce adverse clinical outcome or the occurrence of angiographic restenosis compared with unfractionated heparin/placebo over a period of 6 months.

Effects of heparin and its low molecular weight fractions. Heparin is used routinely during angioplasty to reduce the risk of a thrombotic abrupt vessel closure. However, it is also well

Table 4. Primary Clinical End Points in Treatment Groups

Event	UFH Placebo (n = 306) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]	p Value*
Primary end point	98 (32.0)	102 (33.3)	200 (32.7)	0.707
Occurring on PTCA day				
Death	0 (0.0)	0 (0.0)	0 (0.0)	—
Nonfatal MI	3 (1.0)	4 (1.3)	7 (1.1)	0.673
Repeat PTCA	1 (0.3)	2 (0.7)	3 (0.5)	0.642
CABG	0 (0.0)	0 (0.0)	0 (0.0)	—
Rescue stent implantation	21 (6.9)	6 (2.0)	27 (4.4)	0.003
Occurring after PTCA day				
Death	1 (0.3)	1 (0.3)	2 (0.3)	0.995
Nonfatal MI	4 (1.3)	8 (2.6)	12 (2.0)	0.240
Repeat PTCA	62 (20.3)	74 (24.2)	136 (22.2)	0.245
CABG	6 (2.0)	7 (2.3)	13 (2.1)	0.732
Unknown end point status†	8 (2.6)	3 (1.0)	11 (1.8)	0.105

*Mantel-Haenszel test, adjusted for center. †Counted as success. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

known, at least in the experimental setting, to have antiproliferative actions that may be useful in the prevention of restenosis (25–29). Cell culture data demonstrated that the dose-dependent antiproliferative properties of low molecular weight heparins are more potent and are basically independent of their ability to bind antithrombin III (29). Although the exact mechanism of action of heparin and its low molecular weight fractions for prevention of cell proliferation is not fully understood, the antiproliferative effect of heparin and its analogues appears to be due to the inhibition of thymidine and uridine uptake by smooth muscle cells (26). It is assumed that the glycosaminoglycans provide an important cell regulatory action

Figure 1. Plot of occurrence of clinical events (end points) in the unfractionated heparin (UFH)/placebo and reviparin groups within 210 days of PTCA.

within the arterial wall (27). Reviparin, a low molecular weight heparin, differs from unfractionated heparin in a number of ways (30). It is generated from heparin by chemical depolymerization and has an average molecular weight of 4,300 daltons. The depolymerization process produces widely different products with differences in their microstructure, antithrombin III affinity and the degree of sulfation. Because of the shorter chain length, it has approximately three times more anti-Xa activity than anti-IIa activity in contrast to the 1:1 ratio for heparin.

Experience with heparins in reducing restenosis. Attempts to modify the fibroproliferative response due to angioplasty by pharmacologic interventions have yielded very limited success. Ellis et al. (31) reported that an 18- to 24-h infusion of heparin after PTCA did not prevent restenosis in a randomized trial. In one study (32) using fragmin, a low molecular weight heparin, a significant trend toward a reduction in restenosis was seen. A preliminary brief report (31) of a randomized trial of 10,000 U of subcutaneous heparin once daily compared with placebo was discontinued because of a high incidence of adverse events and angiographic restenosis. One report (33) has even suggested that heparin treatment may promote restenosis. Enoxaparin in a dose of 40 mg/day subcutaneously for 1 month did not reduce the incidence of angiographic restenosis or the occurrence of clinical events over 6 months (34).

Study design. In view of this previous experience, several aspects of the REDUCE trial are noteworthy. The selection of patients with single-lesion dilation was designed to avoid confusion resulting from differences in per patient and per lesion results. Patients with restenosis or myocardial infarction within 14 days of PTCA were excluded to first define the impact of the substance in a population with comparable pathophysiologic substrates. The pharmacologic regimen was based on similar experimental designs, and the dosage was adjusted according to the dosage that resulted in a significant reduction of smooth muscle cell proliferation in the experi-
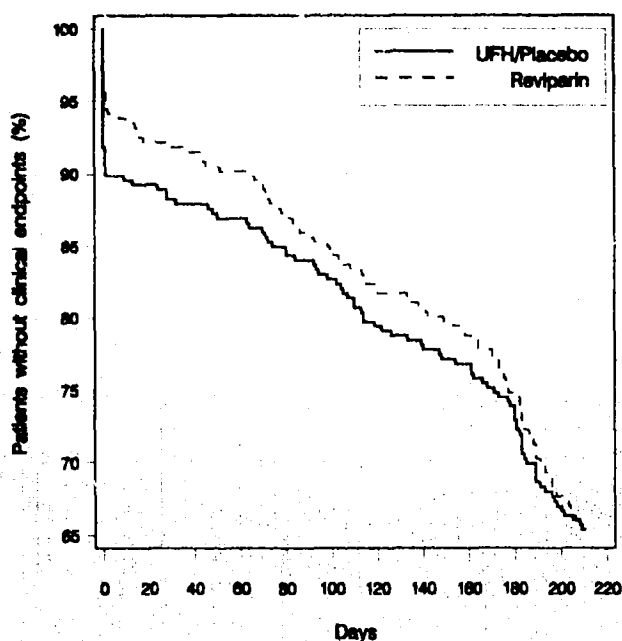
Table 5. Bleeding Complications and Injection Site Hemorrhage in Intention to Treat Cohort

Event	UFH Placebo (n = 300) [no. (%)]	Reviparin (n = 306) [no. (%)]	Total (n = 612) [no. (%)]	p Value*
Major bleeding within 35 days after PTCA	8 (2.6)	7 (2.3)	15 (2.5)	0.8
Injection site hemorrhage	26 (8.5)	12 (3.9)	38 (6.2)	0.065
Decrease in hemoglobin ≥2 g/dl†	62 (20.3)	35 (11.4)	97 (15.8)	0.002

*Mantel-Haenszel test, controlling for center. †Twenty-one patients (12 in the unfractionated heparin placebo group, 9 in the reviparin group) with missing laboratory data. Abbreviations as in Tables 1 and 4

mental setting (16). Despite the high dosages necessary for the antiproliferative effect, the substance was well tolerated at this dosage, without the occurrence of increased bleeding complications. It is of major clinical interest that no monitoring was needed to follow the treatment with reviparin. According to the experimentally documented time course of smooth muscle cell proliferation after vascular injury (8), a specific delivery protocol was adopted. Because the process of smooth muscle cell proliferation begins with the onset of injury and continues for at least 2 weeks, treatment with reviparin was started early and was maintained for a sufficient length of time.

Reasons for lack of benefit. There are many potential reasons for the lack of an effect of reviparin on restenosis: 1) Systemically or subcutaneously injected doses might not have been sufficient to reduce the local arterial proliferative actions. To further evaluate this option, local application with specific local delivery systems (35-37) as well as trials using heparin-coated stents (38) are in the experimental and early clinical stages. 2) The lack of benefit to date shown in nearly all clinical trials of drugs to prevent restenosis that previously were shown to be effective in animal models also raises concerns about the validity of the animal models used to study the restenosis process. 3) Chan et al. (39) have found that cells from patients with restenosis (both restenotic lesion and undiseased vessels) showed significant lower sensitivity to growth inhibition by heparin than control cells (p < 0.001). This relative heparin resistance of human vascular smooth muscle cells may explain why pharmacologic agents that inhibit neointimal proliferation in animal models have failed to prevent human vascular restenosis. In a recent study (40), low molecular weight heparin given in high doses has been ineffective in inhibiting smooth muscle cell proliferation in a baboon model of angioplasty. It is proposed that the lack of an effect in primates might reflect the presence of a heparin-insensitive pathway of smooth muscle cell activation, possibly through platelet-derived growth factor. 4) Restenosis is a multifactorial process, including such factors as vessel recoil and fibrotic contraction, and attempts to prevent it by a single agent focused on a single process may be inadequate.

Acute results. The administration of reviparin as a bolus and infusion resulted in a 52% reduction in the composite acute event rate, primarily in the need for stent implantation as a rescue procedure and in the use of autoperfusion balloon catheters. However, this finding must be counted as an additional observation because early events and acute complications of PTCA were not designed as an end point of the study.

The rather low incidence of 3.9% of early events in the present study is comparable to that found in the Hirudin in a European Restenosis Prevention Trial Versus Heparin Treatment in PTCA Patients (HELVETICA) study (41), which compared the effects of recombinant hirudin as an adjunctive therapy with angioplasty with placebo. A recent trial using a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor (Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications [EPIC] study [42]) suggested that platelet thrombosis plays an important role in the abrupt closure of coronary lesions treated by angioplasty. The positive effect of reviparin on the early adverse outcome after PTCA may be due to improved antithrombotic properties compared with those of standard heparin (11,12).

Conclusions. The ability of reviparin to inhibit vascular smooth muscle growth in vitro and to limit myointimal hyperplasia in animal models of vascular injury is well documented. However, in the present randomized, controlled study, reviparin given at a very early stage of vascular injury, in dosages equal to those used in the animal studies and administered for a sufficient length of time, did not reduce the incidence of clinical restenosis. Explorative analysis revealed a 52% reduction in the acute-phase adverse outcome, revealing a diminished need for immediate subsequent coronary revascularization procedures.

Appendix

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