Safety and Efficacy of Recombinant Hirudin (CGP 39 393) Versus Heparin in Patients With Stable Angina Undergoing Coronary Angioplasty

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Background. **Enhanced thrombin activity has been associated with acute and long-term complications following balloon angioplasty (percutaneous transluminal coronary angioplasty (PTCA). We evaluated, in a 2-to-1 randomized, double-blind trial, the effects of recombinant hirudin, CGP 39 393, relative to unfractionated sodium heparin on periprocedural events, bleeding, early angiographic outcome, and coagulation in 113 patients with stable angina undergoing PTCA.**

Methods and Results. **Prior to PTCA, 20 mg CGP 39 393 was administered as a bolus, followed by continuous infusion at a rate of 0.16 mg · kg^{-1} · h^{-1}, or 10 000 IU sodium heparin was administered as a bolus and continued at a rate of 12 IU · kg^{-1} · h^{-1} for 24 hours. Infusion was adjusted to activated partial thromboplastin time (APTT) levels. ST segment was monitored for 24 hours, and angiograms were analyzed with quantitative technique (QCA). In 74 CGP 39 393– and 39 heparin-treated patients, 132 lesions were dilated. Myocardial infarction and/or emergency coronary bypass surgery occurred in 1 (1.4%) CGP 39 393 patient compared with 4 (10.3%) heparin patients (relative risk, 7.6; 95% confidence interval, 0.9, 65.6). At 24 hours, complete perfusion was present in 91% heparin and 100% CGP 39 393 patients. Significant ST segment displacement was found in 11% of heparin versus 4% of CGP 39 393 subjects. Bleeding occurred only at the puncture site in 4 CGP 39 393–treated patients. QCA did not reveal significant differences between the groups. APTT values were more often in the target range and more stable in CGP 39 393 patients. Levels of thrombin–antithrombin III complexes, prothrombin fragment F_{1+2}, and fibrinopeptide A indicated that CGP 39 393 was an effective inhibitor of thrombin activity.**

Conclusions. **CGP 39 393 can safely be administered to patients undergoing elective PTCA for stable anginal symptoms and may have a more favorable anticoagulant profile than heparin. (*Circulation*. 1993;88[part 1]:2058-2066.)**

KEY WORDS • **anticoagulants** • **coronary artery disease** • **clinical trials**

The major anticoagulant isolated from the salivary secretions of Hirudo medicinalis, hirudin, is a potent inhibitor of thrombin.[1] Thrombin activates clotting factors V and VIII, promotes its own generation, converts soluble fibrinogen into fibrin, and induces fibrin cross-linking.[2-5] In addition, thrombin stimulates platelet aggregation and thus contributes to the formation of a thrombus through different pathways.[6-9]

Specific and selective anticoagulant properties are exhibited by hirudin's recombinant congener CGP 39 393, an irreversible thrombin inhibitor. In vitro, CGP 39 393 was able to block thrombin-dependent platelet activation,[10] while in vivo, CGP 39 393 was proven to be a powerful antithrombotic compound in models of venous, shunt, and arterial thrombosis.[11,12] In a pig model of carotid angioplasty, CGP 39 393 was shown to prevent thrombosis and to have a more potent antithrombotic profile than heparin.[6]

Although infrequent, acute thrombotic coronary occlusion is a major complication of coronary angioplasty that has been associated with the traumatic effect of the balloon imparted to the vessel wall.[13] The balloon-induced arterial injury exposes subendothelial structures, including collagen as well as material from the atheromatous plaque, and generates cell debris that activates the coagulation system. Because of the early, potent, and activating effects of thrombin on the coagulation cascade and platelet activation, specific and complete inhibition of thrombin could prevent the

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formation of a platelet-rich thrombus, the presence of which has been associated with increased risk for restenosis.[14-16] Such an effect could therefore favorably alter the long-term outcome of balloon angioplasty.[17,18] The present randomized, double-blind trial explored the effects of recombinant hirudin, CGP 39 393, relative to unfractionated sodium heparin on periprocedural ischemic events, bleeding complications, early angiographic outcome, and biological markers of hemostasis in 113 patients with stable angina undergoing percutaneous transluminal coronary (balloon) angioplasty (PTCA).

Methods

Selection Criteria

Patients with either single or multivessel coronary artery disease deemed suitable for balloon angioplasty were eligible for this multicenter trial provided they had stable anginal symptoms and were not receiving heparin. The following exclusion criteria applied: previous angioplasty of the same vessel, dilatation of bypass grafts, myocardial infarction within the previous 2 weeks, severe hypertension, history of bleeding, hemostatic disorders, thrombocytopenia, recent surgery or trauma, child-bearing potential or pregnancy, and current use of drugs known to affect coagulation parameters and/or platelet function, with the exception of acetylsalicyl acid.

The study was conducted in full accordance with the principles of the "Declaration of Helsinki" and subsequent amendments as well as with the laws and regulations of the countries in which the research was conducted. Prior to randomization, patients gave their written informed consent according to the requirements of the local institutional review boards.

Treatment Allocation and Trial Medication Administration

Patients were randomly assigned to receive intravenous treatment with either CGP 39 393 (hirudin) or sodium heparin in a double-blind fashion. Allocation of treatment was accomplished by a central telephone service. There were two allocations to hirudin for every one to heparin. In addition to trial treatment, all patients received 250 to 500 mg acetylsalicyl acid per day from PTCA onward until at least 4 weeks after the procedure.

Recombinant desulfato-hirudin CGP 39 393 was supplied by CIBA-GEIGY Ltd, Basel, Switzerland. It was produced and purified in collaboration with GEN Therapeutica Vertiebs GmBH & Co. The compound has the sequence of hirudin variant 1 but lacks sulfate on tyrosine 63. Its specific activity is about 12 000 antithrombin units per mg protein. The molecular weight of CGP 39 393 is 6964 da.

Dry powder (containing CGP 39 393 or matching placebo) was mixed with a solution of outwardly appearing identical appearance containing either unfractionated heparin (Liquemin) or 0.9% saline (placebo). An IV bolus injection of 20 mg CGP 39 393 or 10 000 IU sodium heparin was administered immediately after introduction of the dilatation sheath in the femoral artery. The bolus injection was followed by a continuous IV infusion of CGP 39 393 at a rate of 0.16 $mg \cdot kg^{-1} \cdot h^{-1}$ or sodium heparin at a rate of 12 $IU \cdot kg^{-1} \cdot h^{-1}$. To maintain activated partial thromboplastin time (APTT) levels between 85 and 120 seconds, infusion rates could be adjusted according to APTT levels obtained at 6-hour intervals. Increases in the infusion rate were not allowed to exceed 3 mL/h in both groups. Prolongation of APTT of 85 to 120 seconds corresponds to heparin levels of 0.35 to 0.5 U/mL.

Administration of trial medication was discontinued after repeat coronary angiography at 24 hours. After cessation of the infusion, the APTT was regularly monitored, and the femoral sheath was removed when the APTT had dropped below 60 seconds. Trial medication was discontinued in case of referral for emergency bypass surgery.

Details of Coronary Angiography and PTCA Procedure

Angiograms were obtained in each patient before and immediately after angioplasty and at follow-up angiography at 24 hours. The position of the x-ray gantry prior to PTCA was recorded, and these settings were reproduced after PTCA and at the follow-up angiogram. The angiograms were acquired in such a manner that the obtained images were suitable for quantitative and videodensitometric analyses, ie, without overlap and/or interference of side branches or the guiding catheter. Details of the methodology have been described previously.[19] A fixed table system was used. The same contrast medium at 37°C was used for each film. A 35 mm cinefilm was used at minimum speed of 25 frames per second. The use of nylon catheters was not allowed. After intracoronary administration of nitroglycerin or isosorbide dinitrate, the coronary arteries were filmed in at least two projections, orthogonal whenever possible.

Coronary angioplasty was performed with conventional technique. The size of the balloon was appropriately adjusted to the dimension of the coronary artery to be dilated. The femoral sheath remained in situ until cessation of trial medication after repeat angiography at 24 hours.

Visual, Quantitative, and Videodensitometric Coronary Analyses

Dissections following angioplasty were graded according to the proposals of the National Heart, Lung, and Blood Registry.[20] Perfusion scores were categorized by use of the Thrombolysis in Myocardial Infarction guidelines,[21,22] and the angiographic criterion for intracoronary thrombus was derived from Capone et al.[23]

Quantitative analysis of dilated coronary segments was performed with a validated computer-based CORONARY ANGIOGRAPHY ANALYSIS SYSTEM (CAAS), previously described in detail.[24-26] Briefly, boundaries of a selected coronary artery segment were detected automatically from optically magnified and video digitized regions of interest (512×512 pixels) of a cine-frame. The absolute diameter of the stenosis (in mm) was determined using the guiding catheter as a scaling device. To that end, each individual catheter was measured by a micrometer. Correction for pincushion distortion was made. The computer-derived estimation of the original dimension of the artery at the site of the obstruction was used to define the (interpolated) reference diameter. The percentage diameter and area stenosis as well as the

cross-sectional area (mm^2) were calculated. The length of the lesion (in mm) was determined from the diameter function on the basis of curvature analysis. The area between the actual and reconstructed contours at the obstruction site was defined as the area plaque (expressed in mm^2).

The cross-sectional area at the site of the dilated lesion was also calculated using videodensitometric analysis. Details of this technique have been published previously.[27,28] In brief, the contours of a selected arterial segment were detected as described above. On each scan line perpendicular to the centerline, a profile of brightness is measured. This profile is subsequently transformed into an absorption profile by means of a logarithmic function. The background brightness contribution is estimated by computing the linear regression line through the background points directly adjacent to the detected contours. Subtraction of the background measure then yields the net cross-sectional absorption profile, which, after integration, provides a measure of the cross-sectional area at that particular scan line. This procedure is subsequently repeated for each scan line to obtain a cross-sectional function.

Frames to be analyzed were selected at end diastole to minimize foreshortening. Coronary segments were categorized according to the guidelines of the American Heart Association.[29]

24-Hour ST Segment Monitoring

ST segment amplitude was recorded with an Oxford MR 35 frequency-modulated recorder from the time of randomization until the end of the 24-hour repeat angiography. Two bipolar leads were used, with electrodes placed (1) left, at the level of the fifth intercostal space, mid-axilary line; (2) right, at the level of the fifth intercostal space, mid-axilary line; (3) at the manubrium sterni; (4) left, at the anterior spina iliaca; and (5) left, at the level of the first intercostal space. Nonradiopaque electrodes were used. An ischemic episode was defined as an episode of transient ST segment displacement of at least 0.1 mV, measured 80 milliseconds after the J point, lasting at least 1 minute. Tapes were analyzed visually and by computer.

Coagulation Parameters

The APTT was measured with the CIBA Corning 512 Coagulation Monitor. APTT levels were measured before and at the end of the angiography session and at 6, 12, and 24 hours following the procedure. If APTT levels were below or above therapeutic range (85 to 120 seconds) at 12 hours, trial medication was adjusted, and the APTT measurement was repeated at 18 hours.

Assays for coagulation parameters were obtained prior to and immediately after angioplasty, as well as at 6 and 24 hours after the procedure. All sampling was done from a large antecubital vein by separate puncture without a tourniquet. Platelet count and thrombin-induced aggregation were performed locally. Assays for prothrombin fragment F_{1+2}, fibrinopeptide A, thrombin–antithrombin III complexes, and anti-Xa and anti-IIa were analyzed centrally at the Center for Hemostasis, Thrombosis, Atherosclerosis and Inflammation Research, Academic Medical Centre, Amsterdam, The Netherlands.

Measures of Outcome and Sample Size Determination

Safety was evaluated on the basis of clinical events, including death, myocardial infarction, (emergency) coronary bypass grafting, stent implantation, or repeat angioplasty, as well as major bleeding. The definition of major bleeding was modified from Hull et al[30] and included any intracranial and retroperitoneal bleeding, as well as bleeding at any other site requiring transfusion of at least 2 units of blood.

The efficacy analysis included results of quantitative coronary analysis, the number of ST segment deviations recorded during 24-hour ECG monitoring, and changes in biological markers of coagulation.

No formal sample size calculation was performed. The (prespecified) sample size was based on practical grounds on the basis of serious adverse experiences. If no unacceptable side effects were observed in 80 patients treated with CGP 39 393, the true incidence of such experiences would be <6% (the upper limit of the 95% confidence interval).

Data Analysis

The effects of CGP 39 393 or unfractionated heparin on angiographic and hemostasis parameters were evaluated only in patients who actually received the designated treatment. Three patients treated with CGP 39 393 who, according to appropriate coagulation tests, had unintentionally received small amounts of heparin in addition to hirudin were not included in this part of the (efficacy) analysis.

The relative risk was defined as the ratio of the rate of events in the two treatment groups. Its precision was expressed with 95% confidence intervals calculated according to Greenland and Robins.[31]

Quantitative angiographic measurements were obtained at each site in case of multiple-site angioplasty. Multiple measurements were then averaged to obtain one value of the parameter at issue per patient.

Continuous variables are presented with their mean and SD values, unless otherwise indicated. Because of their asymmetrical distribution, hemostasis parameters are described with their median value and range; comparisons between the two groups were made using Wilcoxon rank-sum test. $P<.05$ (double-sided) was considered significant in all analyses.

Results

Study Population

Trial medication was initially administered to 118 subjects, but administration was discontinued promptly in 5 subjects because PTCA was not pursued for the following reasons: inability to pass the stenotic lesion with the guidewire in 4 patients, and the presence of a previously unrecognized main stem lesion in another patient.

Demographic and angiographic details of the 113 patients in whom angioplasty was attempted are provided in Table 1. Of these, 74 received hirudin and 39 received heparin. The mean age of the patients was 58 years, with range of 35 to 74 years. Approximately 60% of the patients had Canadian Cardiac Society Classification class I or II angina pectoris, while a previous myocardial infarction was present in 39% of the sub-

TABLE 1. Demographic Variables at Baseline per Treatment Group

	CGP 39 393 (n=74)		Heparin (n=39)	
Age, y (SD)	57.3 (8.2)		59.4 (8.7)	
Males	57	(77%)	31	(79%)
Previous MI	30	(41%)	13	(33%)
Diabetes mellitus	5	(7%)	1	(3%)
Hypertension	27	(36%)	9	(23%)
Current smokers	18	(24%)	9	(23%)
CCS functional classification				
I or II	39	(53%)	24	(62%)
III or IV	35	(47%)	15	(38%)
Medication				
Long-acting nitrates	41	(55%)	17	(44%)
β-Blocking agents	58	(78%)	28	(72%)
Calcium antagonists	47	(64%)	28	(72%)
Acetylsalicylic acid	65	(88%)	30	(77%)
Vessel disease				
One	62	(84%)	31	(79%)
Two	11	(15%)	7	(18%)
Three	1	(1%)	1	(3%)
Location of dilated segments				
RCA	21	(26%)	18	(34%)
LAD	34	(42%)	21	(40%)
LCx	26	(32%)	14	(26%)

MI indicates myocardial infarction; CCS, Canadian Cardiac Society; RCA, right coronary artery; LAD, left anterior descending coronary artery; and LCX, left circumflex coronary artery.

jects. Medication used was typical for a group of patients with stable anginal symptoms. There were no clinically relevant or statistically significant differences between the two treatment groups. A total number of 132 segments was dilated.

Clinical Events

Cardiac complications are summarized in Table 2. All events occurred within 24 hours following PTCA. Two patients in the heparin group sustained a periprocedural myocardial infarction; 1 of them had to undergo emergency coronary bypass surgery. In addition, 2 other heparin-treated patients underwent emergency coronary bypass surgery compared with 1 patient in the CGP 39 393 group. Thus, among 39 patients randomized to heparin, 4 (10.3%) experienced a myocardial infarction and/or underwent emergency coronary bypass surgery in the first 24 hours after balloon angioplasty compared with 1 of 74 (1.4%) hirudin-treated patients. Accordingly, the relative risk of a periprocedural event associated with heparin was 7.6 (95% confidence interval, 0.9, 65.6). After discharge, 1 CGP 39 393–treated patient additionally underwent uncomplicated elective coronary bypass surgery 3 weeks after PTCA.

TABLE 2. Clinical Events Following Balloon Angioplasty

	CGP 39 393 (n=74)	Heparin (n=39)
Cardiac complications		
Death	0 . . .	0 . . .
Myocardial infarction	0 . . .	2 (5%)
Emergency bypass surgery	1 (1%)	3 (8%)
Repeat PTCA	0 . . .	0 . . .
Total No. of:		
Events	1 . . .	5 . . .
Patients with events	1 (1%)	4 (10%)
Other events		
Major bleeding	4 (5%)	0 . . .
ST segment displacement*	3 (4%)	3 (8%)

*Excluding patients with cardiac events.

Adverse Experiences

Major bleeding developed only at the arterial puncture site. Because of such a complication, 4 patients treated with hirudin needed blood transfusion of at least 2 units or had to undergo corrective vascular surgery in three instances. Major bleeding was not observed in patients on heparin. One (heparin-treated) patient experienced visual impairment following angioplasty due to cerebral infarction as diagnosed by computed tomography scanning. Other, minor, adverse events, including symptoms related to the use of contrast material as well as vasovagal reaction following removal of the femoral sheath at 24 hours, occurred infrequently and were evenly distributed between the two treatment groups.

There were no adverse hemodynamic effects associated with trial treatment administration. Routine laboratory assessments remained within normal limits, and immunoallergic reactions were not observed.

Visual Assessment of the PTCA Result

Details of the perfusion scores immediately following PTCA and at 24 hours are presented in Table 3. This evaluation was not possible in four distal segments (in 4 patients) because of emergency coronary bypass surgery precluding repeat angiography in 2 patients and total occlusion of a more proximally located dilated lesion in the same coronary artery in the 2 other subjects. Prior to PTCA, complete occlusion was present in 4% of segments in the heparin group. Complete perfusion immediately after PTCA was observed in all lesions in the hirudin group compared with 92% in the heparin group. Similar scoring rates were observed at 24-hour follow-up angiography.

Dissections of the dilated coronary segments were frequently observed after balloon angioplasty and are detailed in Table 4. In the hirudin group, dissections were present in 35% of cases compared with 24% in the heparin-treated patients (difference not significant). Complicated dissections (types C, D, E, and F) occurred in <10% of all dilated lesions.

Evidence for a coronary thrombus was detected in 2 patients, 1 in each treatment group and in both instances at 24-hour angiography.

TABLE 3. TIMI Score Before, Immediately Following, and at 24 Hours After PTCA on a Segmental Basis

	CGP 39 393 (n=79)			Heparin (n=49)		
	Before PTCA	After PTCA	After 24 Hours	Before PTCA	After PTCA	After 24 Hours
Grade 0: no perfusion	. . .	. . .	. . .	4%	4%	2%
Grade 1: minimal perfusion	4%	. . .	. . .	4%	. . .	. . .
Grade 2: delayed perfusion	11%	. . .	. . .	10%	4%	. . .
Grade 3: complete perfusion	85%	100%	100%	82%	92%	91%
Not applicable	. . .	. . .	. . .	. . .	. . .	7%

TIMI indicates Thrombolysis in Myocardial Infarction; and PTCA, percutaneous transluminal coronary angioplasty.

Contour Detection and Densitrometric Analysis

The angiographic (efficacy) analysis is based on parameters collected in 110 patients, of whom 71 were treated with CGP 39 393, and 39 were treated with heparin. There were no significant differences in the various angiographic variables between the treatment groups prior to angioplasty. As a result of PTCA, the mean obstruction diameter increased from 1.0 to 1.7 mm (SD, 0.4), with a concomitant decrease in diameter stenosis from 61% to 39% (SD 8%) in both treatment groups. The reference diameter remained unchanged. There was a slight but nonsignificant increase in lesion severity observed at the 24-hour angiogram compared with the angiogram obtained immediately after balloon angioplasty.

Changes in the various angiographic parameters between the post-PTCA and the 24-hour angiogram observed in the two treatment groups as well as differences between the groups are presented in Table 5. For example, using videodensitometry, the difference in obstruction area of CGP 39 393–treated patients relative to heparin was 0.0 mm^2, with 95% confidence limits of −0.4 to 0.3 mm^2. In a similar fashion, the 95% confidence interval of the difference between the groups included the value zero in every angiographic comparison. Thus, no significant differences in any of these variables could be observed between the two treatment groups. The cumulative distributions of the minimal luminal diameter and the obstruction area in CGP 39 393– and heparin-treated patients are depicted in Figs 1 and 2.

TABLE 4. Dissections After the PTCA Procedure on a Segmental Basis

	CGP 39 393 (n=79)	Heparin (n=49)
No dissection	51 (65%)	37 (76%)
Dissection present	28 (35%)	12 (24%)
Type of dissection		
A	12 (15%)	5 (10%)
B	8 (10%)	4 (8%)
C	7 (9%)	2 (4%)
D	0 . . .	0 . . .
E	1 (1%)	0 . . .
F	0 . . .	1 (2%)

Coagulation Parameters

A graphic representation of the median APTT levels in the two treatment groups is given in Fig 3. Immediately after balloon angioplasty, approximately 50% of patients in the CGP 39 393 group were within the target APTT range compared with only 3% of the heparin-treated patients. In this latter group, 85% of patients had APTT levels above the 150-second limit. After 6 hours, APTT levels remained in the preset range in 44% of the CGP 39 393 group, but at that time, approximately 70% of the heparin-treated patients exhibited APTT levels <85 seconds. This contrast between the two groups did not disappear in the remaining 24-hour study period.

Concentrations of anti-IIa activity, thrombin–antithrombin III complexes, prothrombin fragment F_{1+2}, and fibrinopeptide A are depicted in Table 6. There was wide variation in anti-IIa activity in patients receiving heparin, whereas the median anticoagulant effect in the CGP 39 393 group was relatively stable.

All median thrombin–antithrombin III complexes were below the upper normal limit of 4.6 μg/L in both treatment groups. However, at the end of heparin treatment, at 24 hours, there was a trend toward higher median values compared with CGP 39 393 treatment.

All median prothrombin F_{1+2} values were below the upper normal limit (1.35 nmol/L). Patients receiving CGP 39 393 at the dose tested appeared to have somewhat higher F_{1+2} concentrations following balloon angioplasty and 6 hours thereafter, but none of these differences reached statistical significance. These findings are nevertheless suggestive of enhanced thrombin generation during this time period in CGP 39 393 patients compared to heparin-treated subjects.

In both treatment groups, a large variation in fibrinopeptide A concentration was observed, although the median concentrations remained low. An indication for enhanced levels of fibrinopeptide A was observed at 24 hours in the heparin group, suggesting increased thrombin activity. This was in accordance with the findings of thrombin–antithrombin III complexes but not for prothrombin F_{1+2}.

24-Hour ECG

ST segment deviations could be analyzed in 104 (CGP 39 393, 69; heparin, 35) patients. Reasons for incomplete assessments were emergency coronary bypass surgery in 3, clock error of the recorder in 1, and a calibration error at the beginning of the recording in 2 patients.

TABLE 5. Contour Detection and Densitometry Results: Changes Between the Post-PTCA and the 24-Hour Angiogram per Treatment Group and Differences and 95% Confidence Intervals Between CGP 39 393– and Heparin-Treated Patients

	CGP 39 393 (n=71), mean (SD)	Heparin (n=39), mean (SD)	Difference	Lower 95% CI	Upper 95% CI
Contour detection					
Plaque area, mm^2	0.8 (1.7)	0.3 (1.1)	0.5	−0.1	1.1
Obstruction diameter, mm	0.0 (0.2)	0.0 (0.3)	0.0	−0.1	0.1
Extent of obstruction, mm	0.2 (1.4)	−0.2 (1.0)	0.4	−0.2	0.9
Reference diameter, mm	0.1 (0.2)	0.1 (0.2)	0.0	−0.1	0.1
Diameter stenosis, %	2.6 (7.7)	3.4 (9.5)	−0.9	−4.2	2.5
Symmetry	0.0 (0.2)	−0.1 (0.2)	0.1	0.0	0.2
Videodensitometry					
Obstruction area, mm^2	0.1 (0.7)	0.1 (1.1)	0.0	−0.4	0.3
Reference area, mm^2	0.5 (0.8)	0.5 (0.9)	0.0	−0.4	0.3
Area stenosis, %	2.4 (13.8)	1.7 (15.2)	0.7	−5.1	6.5

Ischemic episodes were observed in 4 patients (11%) in the heparin group (including 1 patient with a myocardial infarction) and 3 patients (4%) in the CGP 39 393 group.

Discussion

Balloon-induced vascular injury is a potent stimulus for platelet activation that may lead to thrombin-mediated thrombosis. This process can be influenced in various ways, as demonstrated previously. The inhibition of thrombin generation by pretreatment with heparin was investigated by Laskey et al[32] in 35 patients undergoing coronary angioplasty in the setting of an intracoronary thrombus. In that trial, prior treatment with large doses of heparin (resulting in activated clotting time >300 seconds) was associated with a high uncomplicated angiographic success rate of 94% and with a decreased incidence of periprocedural coronary arterial thrombosis. In another study, the role of pretreatment with antiplatelet therapy in reducing the likelihood of acute coronary artery thrombosis associated with balloon angioplasty was described by Barnathan et al.[33] In that report of 263 consecutive patients with initially successful angioplasty, patients were classified into three groups based on the type and extent of antiplatelet therapy received before PTCA. Therapy considered included aspirin and dipyridamole, separately or in combination. In a multivariate model, lack of effective antiplatelet therapy was the strongest predictor of thrombus formation, which occurred at 15% of the PTCA sites. Recently, elevated levels of fibrinopeptide A, a biochemical marker of thrombin activity, early after angioplasty have been associated not only with early reocclusion but also with an increased incidence of adverse angiographic as well as clinical outcome during 6-month follow-up.[34]

The current pilot trial evaluated the merits of CGP 39 393 relative to heparin in patients with stable angina undergoing PTCA with acetylsalicyl acid as concomitant therapy in both groups. Treatment with CGP 39 393 resulted in fewer acute cardiac complications than with heparin. Periprocedural complications (myocardial infarction and/or emergency bypass procedure) were observed in only 1 (1.4%) patient treated with CGP 39 393 compared with 4 (10.3%) patients on heparin. The postangioplasty angiographic findings, which demonstrated fewer occlusions and better coronary flow immediately after and at 24 hours following angioplasty in CGP 39 393–treated patients, supported this observation. In addition, fewer patients treated with CGP 39 393 had ST segment deviations associated with left ventricular ischemia than with heparin, even after exclusion of patients who experienced specific cardiac events. In fact, when ischemia was defined as either the occurrence of a cardiac event or ST segment displacement, the risk of such an event associated with heparin amounted to 3.2 (confidence interval, 1.1, 9.3). Although these findings are suggestive of a favorable effect of CGP 39 393 relative compared with heparin as administered, the absolute number of events encountered was small, and it is obvious that confirmation of these findings in larger series is needed.

The results currently obtained with CGP 39 393 treatment compare favorably to other reports. Periprocedural complications in a larger group of patients were reported by Schwartz et al,[35] who randomized 376 angioplasty patients to treatment with a combination of aspirin and dipyridamol or to placebo. Periprocedural events, including Q-wave myocardial infarction and early revascularization with and without Q-wave infarction, occurred in 27 (7.2%) of the patients. Treatment with antiplatelet agents was found to be superior to placebo. Nevertheless, myocardial infarction occurred in 1.6% and surgical revascularization occurred in 5% of patients on antiplatelet therapy. Periprocedural complications have also recently been described in the National Heart, Lung, and Blood Institute PTCA Registry.[36] In the 1985 to 1986 cohort of that registry, the incidence of acute occlusion was 4.9%. Death was observed in 1%, nonfatal myocardial infarction in 4.3%, and emergency bypass surgery in 3.5%. The incidence of the combined events was 7.2%. Recently, in an overview of predictors of coronary artery occlusion during PTCA, abrupt coronary closure was found to occur in 4.7% to 7.3% of cases and was associated with a very high (>30%) incidence of periprocedural myocardial infarction.[37,38] The present study population, however, in-

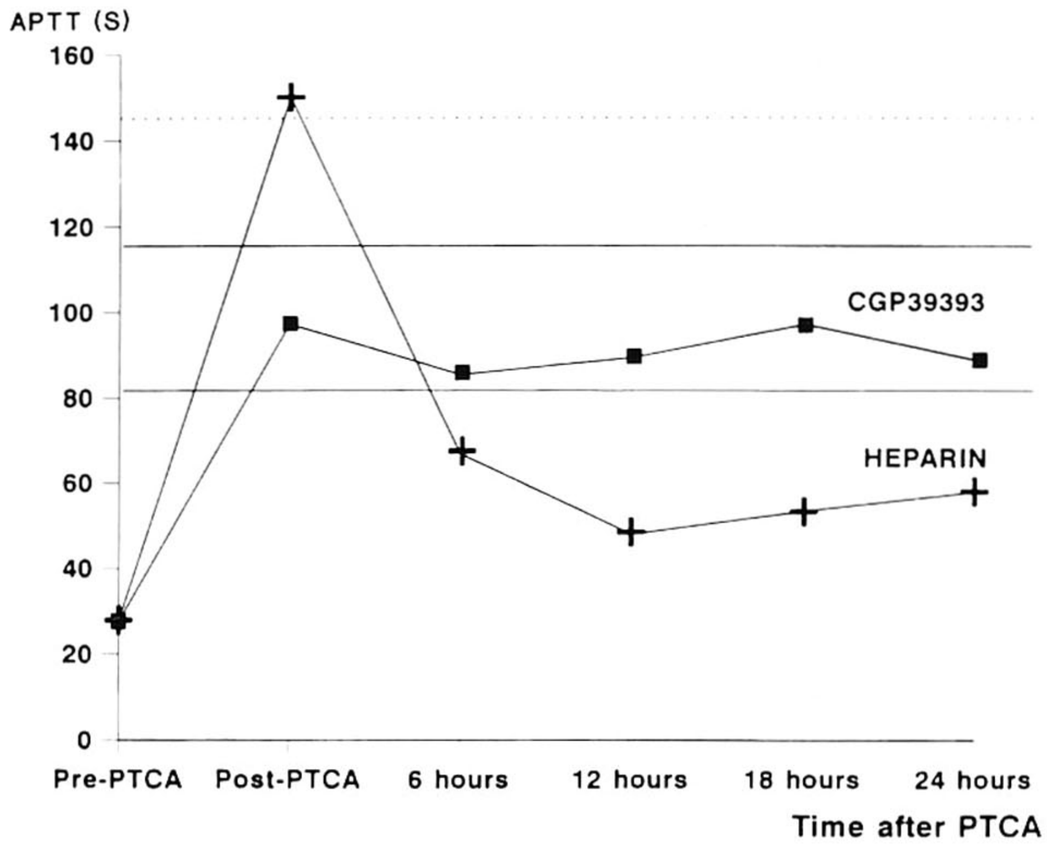

FIG 1. Plot of median levels of activated partial thromboplastin time (APTT) measurements at regular intervals after percutaneous transluminal coronary angioplasty (PTCA) in 74 CGP 39 393– and 39 heparin-treated patients. The horizontal lines indicate target APTT levels (85 to 150 seconds).

cluded only middle-aged patients with stable angina and predominantly one-vessel disease with preserved left ventricular function and should be considered to represent a low-risk group of patients in that respect.

The present findings corroborate evidence obtained in animal models. In the pig model where deep carotid arterial injury was induced by balloon angioplasty, hirudin markedly reduced platelet deposition and completely prevented arterial thrombosis by interfering with the formation of fibrin.[6] In a dose-dependent manner, hirudin has also been demonstrated to interrupt platelet and fibrin deposition on other thrombogenic surfaces, including the endarterectomized aorta in baboons.[3] In addition, thrombotic occlusion in this model was prevented by hirudin but not by heparin, indicating an important mediating role for hirudin in acute thrombus formation. However, this antithrombotic benefit was associated with some impairment of hemostatic function.

Bleeding was more often observed with CGP 39 393 than with heparin. However, the absolute number of bleeding events observed was small, and the number of bleedings requiring blood transfusion or surgical repair (4%) did not exceed the numbers reported in other settings. For example, in the study described by Ellis et al,[39] administration of heparin was continued for 18 to 24 hours after initially successful angioplasty in 208 patients. Major bleeding, although not specified, occurred in 2 patients, while a decrease in plasma hemoglobin of at least 3 g/dL was observed in 17 (8%) patients. In addition, heparin had to be discontinued due to bleeding in 8 other patients. Because of the specific nature of the current trial, involving PTCA followed by repeat angiography at 24 hours using a relatively large (8F) femoral arterial catheter that remained in situ for at least 24 hours, the absolute number of bleedings at the puncture site cannot easily be compared with findings obtained in other trials.

Clinically relevant bleedings were observed only at the site of the femoral arterial sheath. Although APTT levels are affected in a different way by the current two treatment regimens and therefore may not be comparable, it should be emphasized that CGP 39 393–treated patients had higher APTT levels at 24 hours, at which time the arterial femoral sheath was removed. On the other hand, anti-IIa activity in the heparin recipients was higher during the entire 24-hour study period. Biochemical markers of coagulation suggested a more constant suppression by hirudin. It should be realized, however, that the selected heparin regimen that resulted in a less-than-optimal heparinization in a substantial number of patients in the latter half of the study period could have affected the outcome in that treatment group.

Other adverse events were evenly distributed between the two treatment groups and occurred infrequently. Most of these events were related to the invasive angiographic procedure and its subsequent components, such as the use of contrast material and the sometimes painful removal of the femoral sheath.

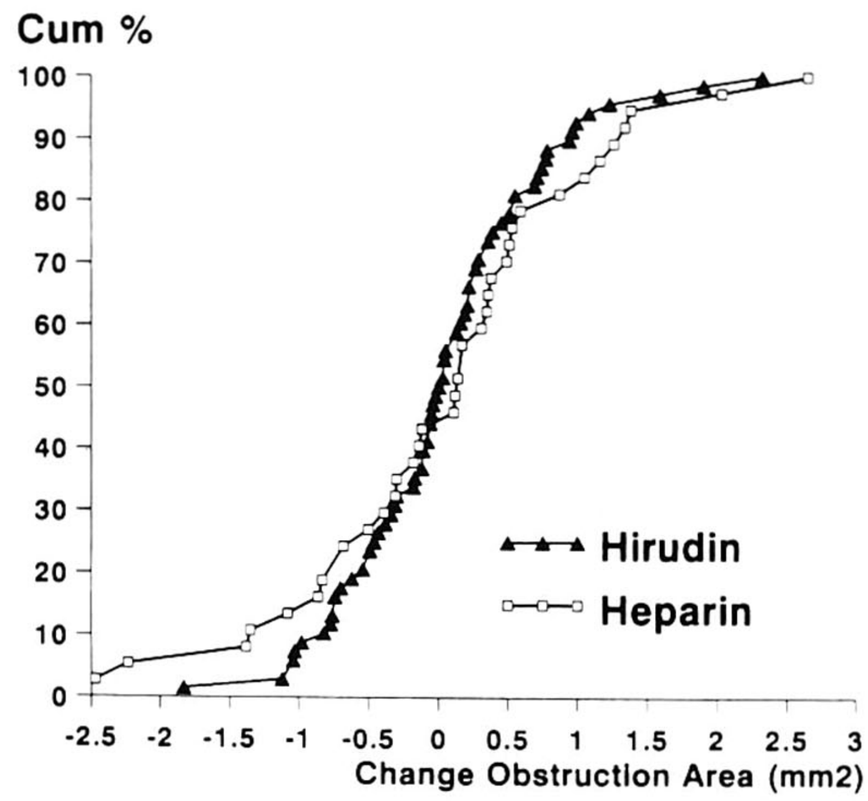

FIG 2. Plot of change in obstruction area quantitatively measured from angiograms obtained immediately following and 24 hours after percutaneous transluminal coronary angioplasty (PTCA) in 71 CGP 39 393– and 37 heparin-treated patients.

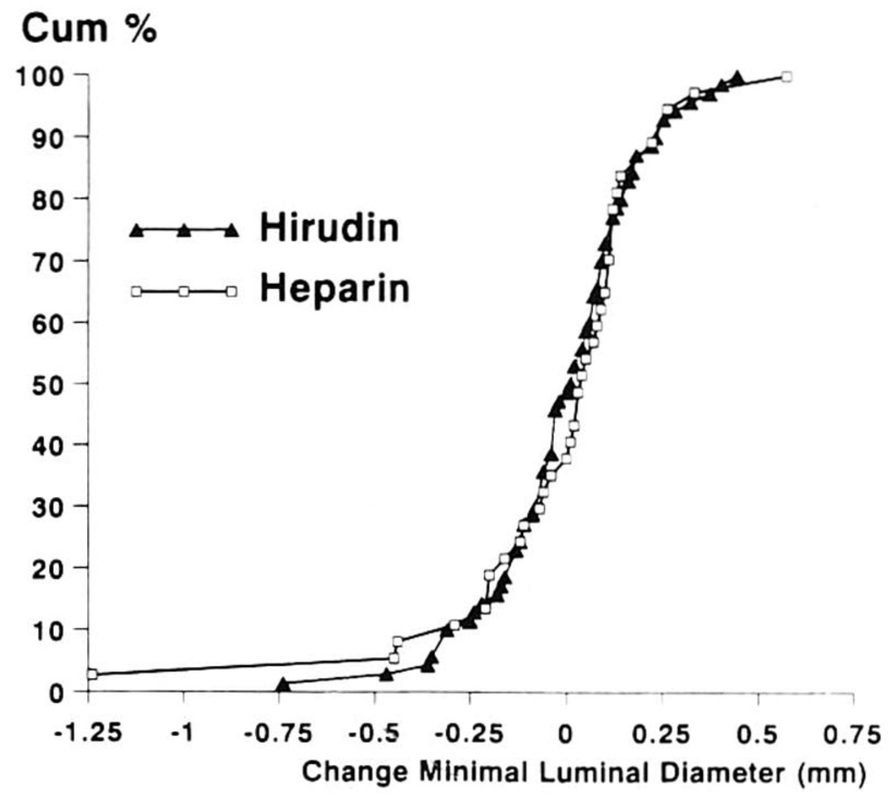

FIG 3. Plot of change in minimal lumen diameter from angiograms obtained immediately following and 24 hours after percutaneous transluminal coronary angioplasty in both treatment groups.

TABLE 6. Median Values (Ranges) of Coagulation Parameters Before, After, and 6 and 24 Hours After PTCA

	Before PTCA	After PTCA	After 6 Hours	After 24 Hours
anti-IIa (μg/L)				
Heparin	0 (0-15)	5978 (1620-10 700)	2488 (0-5790)	1970 (0-6460)
CGP 39 393	0 (0-569)	1418 (220-11 600)	1260 (74-10 200)	1245 (67-10 001)
TAT (μg/L)				
Heparin	2.2 (0.3-61)	2.65 (0.7-61)	2.7 (1.1-61)	3.6 (1.9-61)
CGP 39 393	2.5 (1.1-61)	3.4 (1.2-61)	2.5 (0.9-61)	2.9 (0.9-61)
F_{1+2} (nmol/L)				
Heparin	0.945 (0.17-11)	0.795 (0.21-11)	0.8 (0.23-11)	0.855 (0.33-8.13)
CGP 39 393	0.91 (0.16-11)	1.015 (0.31-11.3)	0.95 (0.19-3.09)	0.955 (0.2-6.23)
FPA (μg/L)				
Heparin	11.65 (1.6-54.8)	4.6 (1.4-41)	5.25 (1.7-47.9)	8.4 (1.8-41)
CGP 39 393	8 (1.5-41)	5.6 (0.5-65)	4 (0.7-27.9)	5.5 (0.4-51.3)

PTCA indicates percutaneous transluminal coronary angioplasty; TAT, thrombin–antithrombin III complexes; F_{1+2}, prothrombin fragment 1 and 2; and FPA, fibrinopeptide A.

One serious adverse experience involved a patient treated with heparin who experienced a nonhemorrhagic stroke shortly after the second angiogram. Most likely, this adverse experience was procedure related.

Conclusions

On the basis of the findings presented herewith, it is concluded that CGP 39 393 can safely be administered in patients with stable angina pectoris undergoing elective balloon angioplasty. Study of coagulation parameters demonstrated CGP 39 393 to be an effective inhibitor of thrombin activity with relatively stable anticoagulant activity during continuous administration. Because of the pivotal role of thrombin in the activation of factors considered to be of importance in the restenosis process, the results of the present trial uncovered the need of a larger trial to assess the efficacy of CGP 39 393 in preventing cardiovascular clinical events as well as angiographic restenosis in patients undergoing PTCA.

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