

Prevention of Restenosis After Percutaneous Transluminal Coronary Angioplasty With Thromboxane A₂-Receptor Blockade

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background. GR32191B is a novel thromboxane A₂-receptor antagonist with potent antiaggregational and antivasoconstrictive properties. We have conducted a randomized, double-blind, placebo-controlled trial to study its usefulness in restenosis prevention.

Methods and Results. Patients received either GR32191B (80 mg orally before angioplasty and 80 mg/day orally for 6 months) or 250 mg i.v. aspirin before angioplasty and placebo for 6 months. Coronary angiograms before angioplasty, after angioplasty, and at 6-month follow-up were quantitatively analyzed. Angioplasty was attempted in 697 patients. For efficacy analysis, quantitative angiography at follow-up was available in 522 compliant patients (261 in each group). Baseline clinical and angiographic parameters did not differ between the two treatment groups. The mean difference in coronary diameter between postangioplasty and follow-up angiogram (primary end point) was -0.31 ± 0.54 mm in the control group and -0.31 ± 0.55 mm in the GR32191B group. Clinical events during 6-month follow-up, analyzed on intention-to-treat basis, were ranked according to the highest category on a scale ranging from death (control, six; GR32191B, four) to nonfatal infarction (control, 22; GR32191B, 18), bypass grafting (control, 19; GR32191B, 22) and repeat angioplasty (control, 52; GR32191B, 48). No significant difference in ranking was detected. Six months after angioplasty, 75% of patients in the GR32191B group and 72% of patients in the control group were symptom free.

Conclusions. Long-term thromboxane A₂-receptor blockade with GR32191B does not prevent restenosis and does not favorably influence the clinical course after angioplasty. (*Circulation* 1991;84:1568-1580)

Percutaneous transluminal coronary angioplasty (PTCA) is increasingly being used as an alternative to coronary artery bypass graft surgery in patients with coronary artery disease.

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Although major improvements in angioplasty techniques have resulted in a high initial success rate, the late restenosis rate of 20-40% still limits the long-term benefit of the procedure.¹⁻⁵ For multivessel angioplasty, the restenosis percentage is even higher.⁶ It is well known that restenosis after balloon angioplasty is a time-related phenomenon, occurring in the first months after balloon angioplasty.^{5,7} Only very rarely does restenosis present itself more than 6 months after coronary angioplasty^{8,9}; therefore, the follow-up period has been limited to the first six months after angioplasty in the current trial.

Deendothelialization and vascular disruption at the angioplasty site expose vessel wall smooth muscle cells and collagen directly to blood. This causes platelet adhesion, platelet aggregation, and activation of the clotting cascade. In addition, platelets may

also activate leukocytes to release vasoconstrictor leukotrienes. These effects appear to be thromboxane mediated as inhibition of thromboxane reduces leukocyte activation.¹⁰ Adhesion and aggregation of platelets at the postangioplasty plaque can lead to an early occlusion within the first 48 hours after angioplasty. Over the long term, platelet- and monocyte-derived growth factors stimulate smooth muscle cell proliferation, leading to the fibroproliferative reaction of the vessel wall in the first months after balloon angioplasty.¹¹⁻¹³ Apart from the proliferation process, organization of mural thrombi may also be the cause of restenosis.^{14,15} Early platelet aggregation thus appears to play a pivotal role in the occurrence of postangioplasty thrombotic occlusion and the restenosis process.¹⁶

Thromboxane A₂ (TXA₂) is a potent platelet aggregational agent and vasoconstrictor released from activated platelets. Beyond the platelet-activating effect, TXA₂ also appears to have a more direct effect on vascular smooth muscle cell proliferation. Using primary cultures of smooth muscle from rat aorta, Hanasaki et al¹⁷ demonstrated a mitogenic effect of thromboxane on smooth muscle cells, which occurs through binding to its specific receptor and may be suppressed by thromboxane-receptor blockade,¹⁷ a promising approach to the inhibition of the effects of TXA₂.¹⁸ TXA₂-receptor blockade prevents the deleterious actions of TXA₂ while sparing the beneficial synthesis of prostacyclin. GR32191B has been shown to be a potent and specific TXA₂-receptor-blocking drug that antagonizes the proaggregatory, vasoconstrictor, and bronchoconstrictor actions of TXA₂, as well as those of agents that act indirectly via TXA₂, such as collagen and arachidonic acid, and agents that directly stimulate the receptor, such as prostaglandin H₂ and the TXA₂ mimetic U-46619.^{18,19} Although not affecting platelet adhesion, it potently inhibits the aggregation of platelets onto damaged blood vessels.^{18,20} This property, together with the ability of the compound to inhibit the platelet-release reaction, indicates a potential clinical use of GR32191B in reducing early thrombotic events, late intimal hyperplasia, and subsequent restenosis after coronary angioplasty. The present multicenter, randomized, double-blind, placebo-controlled trial (Coronary Artery Restenosis Prevention on Repeated Thromboxane-Antagonism [CARPORT]) was carried out to evaluate the role of GR32191B in the prevention of late restenosis after PTCA.

Methods

All patients with angina and angiographically proven coronary artery disease who were scheduled for angioplasty were considered for inclusion at one of six participating centers (see "Appendix"). The trial was carried out according to the declaration of Helsinki, and specific exclusion criteria are given in Table 1. A screening log was maintained in two centers. At these two centers, 1,614 patients were

TABLE 1. Reasons for Exclusion for 1,318 of 1,614 Screened Patients at Two of Six Participating Centers

Reason	n	Total (%)
Insufficient lead-in time*	235	18
Use of platelet-inhibiting or nonsteroidal anti-inflammatory drugs within 7 days preceding the study	352	27
Refusal to participate and/or undergo 6-month recatheterization	364	28
Currently taking oral anticoagulant drugs	119	9
Angioplasty for restenosis	105	8
Acute myocardial infarction within 2 weeks preceding angioplasty	52	4
Bypass graft dilatation	39	3
History of obstructive airway disease	26	2
History of peptic disease or upper gastrointestinal bleeding	10	1
Previous participation in the trial	2	0.2
Severe other disease	6	0.5
Participation in another trial	6	0.4
History of intolerance to aspirin	1	0.1
Less than 21 years old	1	0.1
Pregnant woman or woman likely to become pregnant during study	0	0
Total	1,318	100

*Urgent referrals outside working hours.

screened from December 1987 through June 1989, and 72% were excluded (Table 1).

Randomization and Treatment Protocol

Randomized, double-blind trial medication was allocated by telephone after the patient had been registered at the central allocation service. Trial medication consisted of either GR32191B for 6 months or control treatment with one dose of aspirin, followed by matching placebo.

One hour before angioplasty, patients allocated to GR32191B received 4 tablets of 20 mg GR32191B orally and an intravenous injection of a physiological salt solution. Patients allocated to control treatment received 250 mg i.v. acetylsalicylic acid and 4 placebo tablets. In addition to trial medication, all patients received a bolus of 10,000 units i.v. heparin at the beginning of the procedure. After two hours, 5,000 units/hr was given for as long as the procedure continued. Also, all patients received 10 mg nifedipine every 2 hours for the first 12 hours and 20 mg slow-release nifedipine tablets thereafter every 8 hours up to the second day after angioplasty.

In those patients in whom angioplasty was successful, either 40 mg GR32191B twice daily or placebo was started in the evening and continued until the end of follow-up. The final dose of trial medication was taken 1 hour before the follow-up angiogram. In addition, all participants were provided with paracetamol in 500-mg tablets for use as analgesic and were asked to avoid acetylsalicylic acid or nonsteroidal anti-inflammatory drugs while on trial medication.

Trial medication and paracetamol were packaged and supplied by Glaxo Group Research, which also prepared the random plan. Randomization was stratified by center.

Angioplasty Procedure and Follow-up Angiography

Coronary angioplasty was performed with a steerable, movable guide wire system via the femoral route. Choice of balloon type and brand as well as inflation duration and pressure were left to the operator. For the purpose of the study, three coronary angiograms were obtained in each patient—one just before angioplasty, one immediately after angioplasty, and one at follow-up. Angiograms were recorded in such a way that they were suitable for quantitative analysis by the coronary angiography analysis system (CAAS), using fixed-table systems and 35-mm cinefilm at a minimum speed of 25 frames/sec. All necessary details of the procedure were recorded in the case record form, and drawings of the segments to be analyzed were made by the investigators. Before the postangioplasty angiogram, radiopaque guide wires had to be removed to avoid interference with automated edge detection. For calibration purposes, catheter tips were cut off and sent with the cinefilm to the angiographic core laboratory. To standardize the method of data acquisition and to ensure exact reproducibility of postangioplasty and follow-up angiograms, measures were undertaken as has been described earlier.^{5,21,22} A qualitative assessment of certain lesion characteristics was performed (see Table 2). Intracoronary thrombus was defined as the presence of a filling defect within the lumen, surrounded by contrast material seen in multiple projections in the absence of calcium within the filling defect, the persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream. Haziness was defined as a small radiolucent area within the lumen of the vessel disappearing with the passage of contrast material (type A dissection according to Dorros et al²³). Intimal tear was defined as a filling defect within the lumen and dissection as contrast appearing outside the lumen, disappearing or persisting with the passage of contrast material (types B and C dissections according to Dorros et al²³).

Follow-up Evaluation

After successful angioplasty, defined as at least one lesion successfully dilated (i.e., less than 50% diameter stenosis on visual inspection after the procedure) as judged by the investigator, patients returned to the outpatient clinic after 3 weeks and 3, 6, and 7 months for an interview, a physical examination, laboratory tests, a tablet count, and, except for the 6- and 7-month visits, a new supply of trial medication. Patients with an unsuccessful angioplasty discontinued trial medication and received the standard medical care. The follow-up clinical status of all patients, irrespective of PTCA success, was assessed 6 months after the procedure. In one of the participating

TABLE 2. Angiographic Baseline Data of Compliant Patients With Quantitative Angiographic Follow-up

	Control (n=261)		GR32191B (n=261)	
	n	%	n	%
Lesions (n)	320		316	
Lesions per patient (n)	1.23		1.21	
Vessels dilated				
LAD	167	52	146	46
RCA	90	28	99	31
LCx	63	20	71	23
Calcified lesion	19	6	32	10
Discrete	242	76	239	76
Asymmetry	133	42	134	42
Total occlusion	12	4	10	3
Tandem lesion	25	8	24	8
Side branch in stenosis	99	31	78	25
Side branch in dilatation site	178	56	193	61
Inflation duration (seconds)	138±92		133±90	
Maximum inflation pressure (atm)	9±2		9±2	
Balloon-to-artery ratio	1.10±0.22		1.06±0.22	
Thrombus visible after angioplasty	7		12	
Dissection	49	15	46	15
At balloon site	44		39	
Proximal of balloon	1		1	
Distal of balloon	4		6	
Intimal tear	37	12	26	8
Haziness	45	14	56	18

LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex artery.

centers (Rotterdam), platelet aggregation tests, using ADP and U-46619 (a TXA₂ mimetic) as aggregants, were carried out to assess pharmacological activity of the drug. At 6-month follow-up, 1–4 days before angiography, a symptom-limited exercise test was performed on a bicycle ergometer according to two different protocols. In Berlin, the test was performed with the patient in a supine position, starting with a work load of 25 W, which increased by 25 W every 2 minutes. In the other clinics, the test was performed with the patient in a sitting position, starting with a work load of 20 W, which was increased by 20 W every 1 minute. Exercise was continued until anginal symptoms, a drop in systolic blood pressure, severe arrhythmia, or a ST depression of more than 1 mm occurred. A 12-lead electrocardiogram was recorded during exercise and recovery. ST changes were measured 80 msec after the J point. Horizontal or downsloping ST segment depression associated with anginal symptoms was considered a positive response to the stress test. The follow-up coronary angiogram was performed at the 6-month visit. If symptoms recurred within 6 months, coronary angiography was carried out earlier. If no definite restenosis was

present and the follow-up time was less than 4 months, the patient was asked to undergo another coronary arteriogram at 6 months.

Quantitative Angiography

All cineangiograms were analyzed using the CAAS system, which has been described in detail.²⁴⁻²⁶ A computer-derived reconstruction of the original arterial dimension at the site of obstruction (assuming there is no disease present) is used to define the interpolated reference diameter. The absolute values of the stenosis diameter as well as the reference diameter are measured by the computer using the known contrast catheter diameter as a scaling device. Because the algorithm is not able to measure total occlusions, a value of 0 mm was substituted for the minimal lumen diameter and 100% for the percent diameter stenosis. In these cases, the postangioplasty reference diameter was substituted for the reference diameter before angioplasty. In contrast, for a totally occluded vessel at follow-up angiography, a value was not substituted, so that the change in reference diameter from after angioplasty to follow-up was only calculated when an actual measurement was available.

Balloon-to-artery ratio was defined as the ratio of the mean balloon diameter measured in a single nonforeshortened projection and the reference diameter of the dilated segment in the same projection.

Assay of GR32191B and Platelet Aggregation Tests

Plasma samples of patients allocated to active drug treatment were taken before first drug intake and approximately 1 hour afterward. These samples were analyzed for GR32191B by high-performance liquid chromatography with fluorescence detection after solid-phase extraction on an advanced automated sample processor.

For the aggregation tests, blood was drawn from the patient by venipuncture. Nine parts of blood were mixed with 1 part 0.13 M sodium citrate solution. The blood was then centrifuged (15 minutes at 200g at room temperature), and the supernatant platelet-rich plasma (PRP) was carefully removed using a plastic Pasteur pipette and transferred to a separate plastic tube. The remaining blood was centrifuged for 10 minutes at 2,000g at room temperature to obtain platelet-poor plasma (PPP). PPP was then added to PRP to obtain PRP with a platelet count of 200×10^9 platelets/l. The PRP was stored at room temperature in full, capped tubes (contents, 5 ml) for 30–90 minutes. Aggregation was performed in a Payton twin-channel aggregometer at 37°C with a stirring speed of 900 rpm. Maximum and minimum light transmission was set up using PPP and PRP, respectively. Samples of 400 μ l PRP were incubated in the aggregometer for 3 minutes at 37°C, and 40 μ l of either the TXA₂ mimetic U-46619 (final concentration, 1 μ M) or ADP (final concentration, 10 μ M) was added. Aggregation was allowed to proceed to its maximum or a period of 5 minutes was allowed,

whichever was longer. Aggregation was expressed as the peak response and represented in millimeters.

End Points

The primary end point of the present study was the within-patient change in minimal lumen diameter as determined by quantitative angiography after PTCA and at follow-up. Post-PTCA values were obtained from the last post-PTCA angiogram made before withdrawal of the guide catheter. The initial procedure were considered finished when the guide catheter was removed. In case evolution of the clinical condition required repeat PTCA (with reinsertion of guide catheter), the angiogram made before repeat balloon inflations was used to obtain follow-up values, regardless of the timing of repeat PTCA (hours, days, or weeks). Otherwise, the follow-up angiogram made according to protocol was used. For each dilated segment, the post-PTCA and follow-up minimal lumen diameters were taken as the mean values from multiple matched projections. Within-patient change (i.e., the primary end point) was defined as the follow-up minus the post-PTCA value. In case more than one segment was dilated (multivessel or multisite procedures), the change in minimal luminal diameter per patient was calculated as the average of the different lesions. Secondary end points were clinical events believed to be related to restenosis. These were death (regardless of cause), nonfatal myocardial infarction (at least two of the following: typical pain, electrocardiographic changes suggesting acute myocardial infarction, cardiac enzymes more than twice the upper limit of normal), coronary artery bypass graft surgery (CABG), and repeat angioplasty at the same site. Events were classified as “procedural” (i.e., onset of event or decision to perform another procedure taken while the guide catheter was still in place), “early” (i.e., onset within 24 hours of guide catheter removal), or “late” (i.e., onset more than 24 hours after guide catheter removal). Another secondary end point was the presence and severity of angina pectoris as assessed by the Canadian Cardiovascular Society classification at last follow-up.

Statistical Methods and Analysis

The minimal sample size was estimated at the outset of the study to be 233 patients in each group on the assumption of a change of -0.40 ± 0.50 mm in mean minimal lumen diameter between postangioplasty and follow-up angiogram in the control group⁵ and -0.25 ± 0.50 mm (i.e., a 30% difference) in the active drug group (two-sided test with an α error of 0.05 and a power of 0.90).

In the comparison between treatment groups for the primary angiographic end point, patients included were those who had a successful initial angioplasty, had a quantitatively analyzable PTCA angiogram, had follow-up angiogram made while on trial medication, and were compliant with trial medication (had used at least 80% of their trial medication during the intervening period and had not discontin-

TABLE 3. Clinical Baseline Data of 697 Patients Included in Analysis for Clinical End Points

	Control (n=346)		GR32191B (n=351)	
	n	%	n	%
Men (n)	276	80	279	80
Age (years)	56.9±9.0		56.6±9.0	
Ever smoked	259	75	280	80
Current smoker	40	12	57	16
Diabetes	28	8	29	8
History of hypertension	111	32	120	34
Lipids (mmol/l)				
Total cholesterol	6.2±1.1	(n=337)	6.2±1.2	(n=345)
LDL cholesterol	4.2±1.2	(n=240)	4.1±1.3	(n=251)
HDL cholesterol	1.1±0.5	(n=290)	1.2±0.5	(n=297)
CCS class				
I	37	11	42	12
II	111	32	116	33
III	141	41	140	40
IV	57	16	52	15
Pain at rest controlled by intravenous nitrates	43	12	48	14
Duration of angina (months)	2±44		24±45	
Previous MI	134	39	132	38
Previous CABG	7	2	12	3
Previous angioplasty	4	1	6	2
Patients on medication				
Nitrates	235	68	225	64
Calcium antagonists	208	60	222	63
β-Blockers	175	51	191	54
Monotherapy	97	28	104	30
Double therapy	151	44	156	44
Triple therapy	73	21	74	21

LDL, low density lipoprotein; HDL, high density lipoprotein; CCS, Canadian Cardiovascular Society angina classification; MI, myocardial infarction; CABG, coronary artery bypass graft surgery.

ued trial medication for more than 3 days). To test the null hypothesis that both mean changes in minimal lumen diameter are equal, an unpaired *t* test was used and a 95% confidence interval for the effect measure was obtained.

Comparisons for each clinical event were made on the basis of intention to treat (i.e., with inclusion of all patients who were randomized—defined as having taken at least their initial oral dose of trial medication—and regardless of angioplasty outcome or trial medication compliance). Also, the clinical status of each patient at the end of follow-up was ranked by assignment to the lowest applicable category of the following ordinal scale: 1, death; 2, nonfatal myocardial infarction; 3, status after CABG; 4, status after repeat PTCA; 5, presence of angina pectoris (Canadian Cardiovascular Society classification of 1 or higher); and 6, none of the above. The percentages of patients in each of these categories were compared between treatment groups on the basis of intention to treat. For all comparisons, the null hypothesis of no difference was tested by appropriate statistical tests.

Results

A total of 707 patients were randomized. Of these patients, 353 were randomized to receive GR32191B, and 354 were randomized to the control group. Selected demographic, clinical, and angiographic characteristics of the two study groups are shown in Tables 2 and 3. No baseline differences were observed between the two groups.

Figure 1 shows the patient flow and the reasons that subjects could not be evaluated with respect to quantitative angiographic restenosis. In 10 patients, angioplasty was not performed. One patient, who could not be treated because of radiographic equipment failure, was rerandomized 2 weeks later and retrospectively excluded as a protocol violator (previous participation in the trial was an exclusion criterion). Angioplasty was successful in 322 of the treated patients and 327 of the control group. Angioplasty was unsuccessful in 29 patients in the treated group and 19 in the control group. Thus, 322 treated patients and 327 control patients underwent successful angioplasty of at least one lesion and were eligible for follow-up angiography. Quantitative angiographic

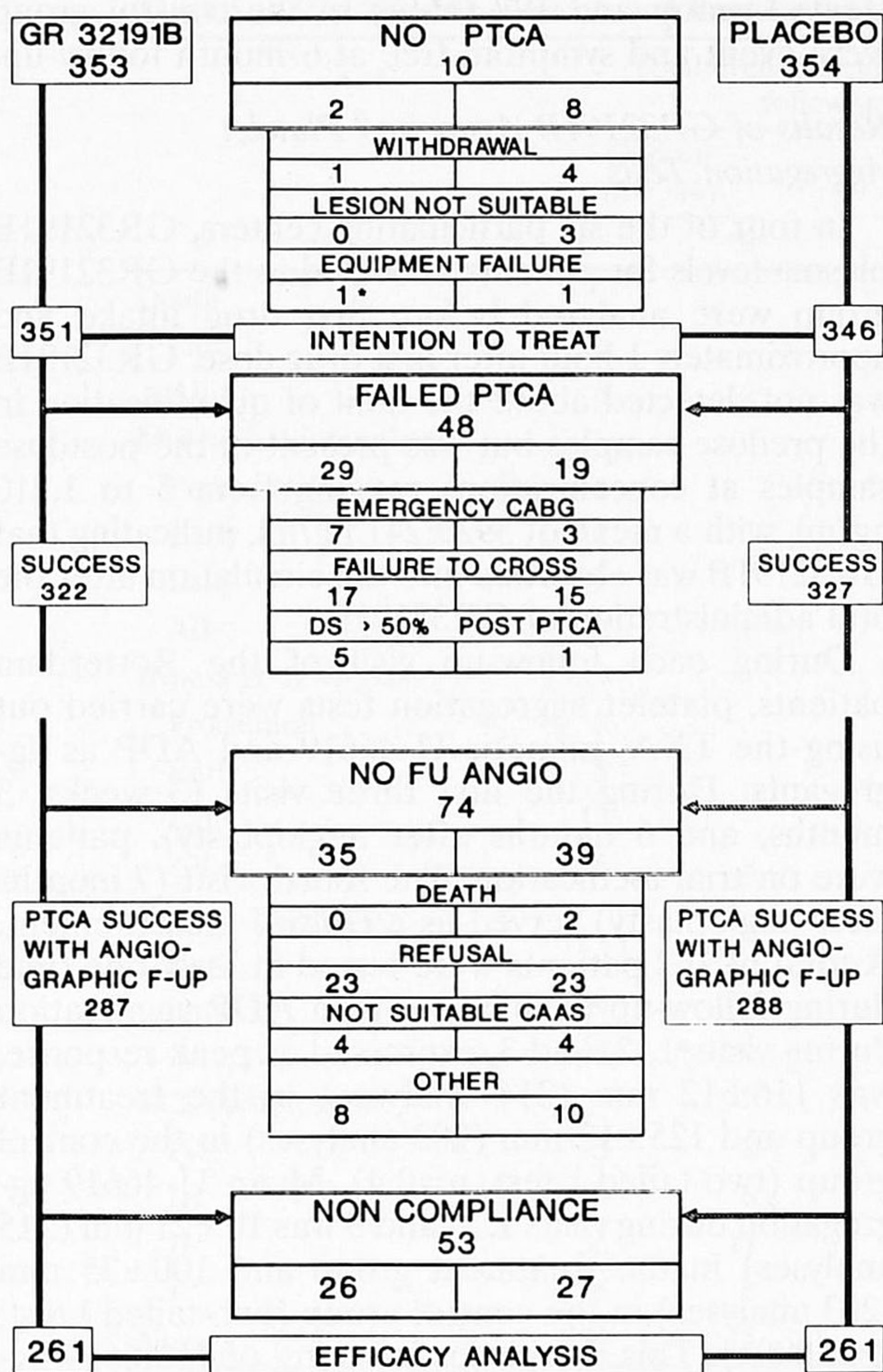


FIGURE 1. Schematic of patient flow in Coronary Artery Restenosis Prevention on Repeated Thromboxane-Antagonism trial and reasons why no follow-up angiogram and/or quantitative angiography was obtained. Angio, coronary angiography; CABG, coronary artery bypass graft surgery; CAAS, coronary artery analysis system; DS, diameter stenosis; FU, follow-up; angioplasty, percutaneous transluminal coronary angioplasty. *Patient randomized twice and excluded from trial.

follow-up as not available in 74 cases (35 treated and 39 control). In 18 cases, quantitative angiography could not be obtained for a variety of reasons: peripheral vascular problems ($n=3$), intercurrent noncardiovascular disease rendering repeat catheterization not desirable ($n=9$), one patient moved to another country, three patients underwent CABG without preoperative recatheterization, one cinefilm was lost, and one film was damaged during processing. Finally, 53 patients did not fulfill the compliance criteria and were excluded from the quantitative angiographic efficacy analysis (Figure 1).

Result of Angiographic Efficacy Analysis

Table 4 and Figure 2 summarize the quantitative angiographic findings of the efficacy analysis. At follow-up, the loss of minimal lumen diameter was identical in both groups: -0.31 mm (treatment effect, 0 mm; 95% confidence intervals, -0.09 , 0.09). Figure

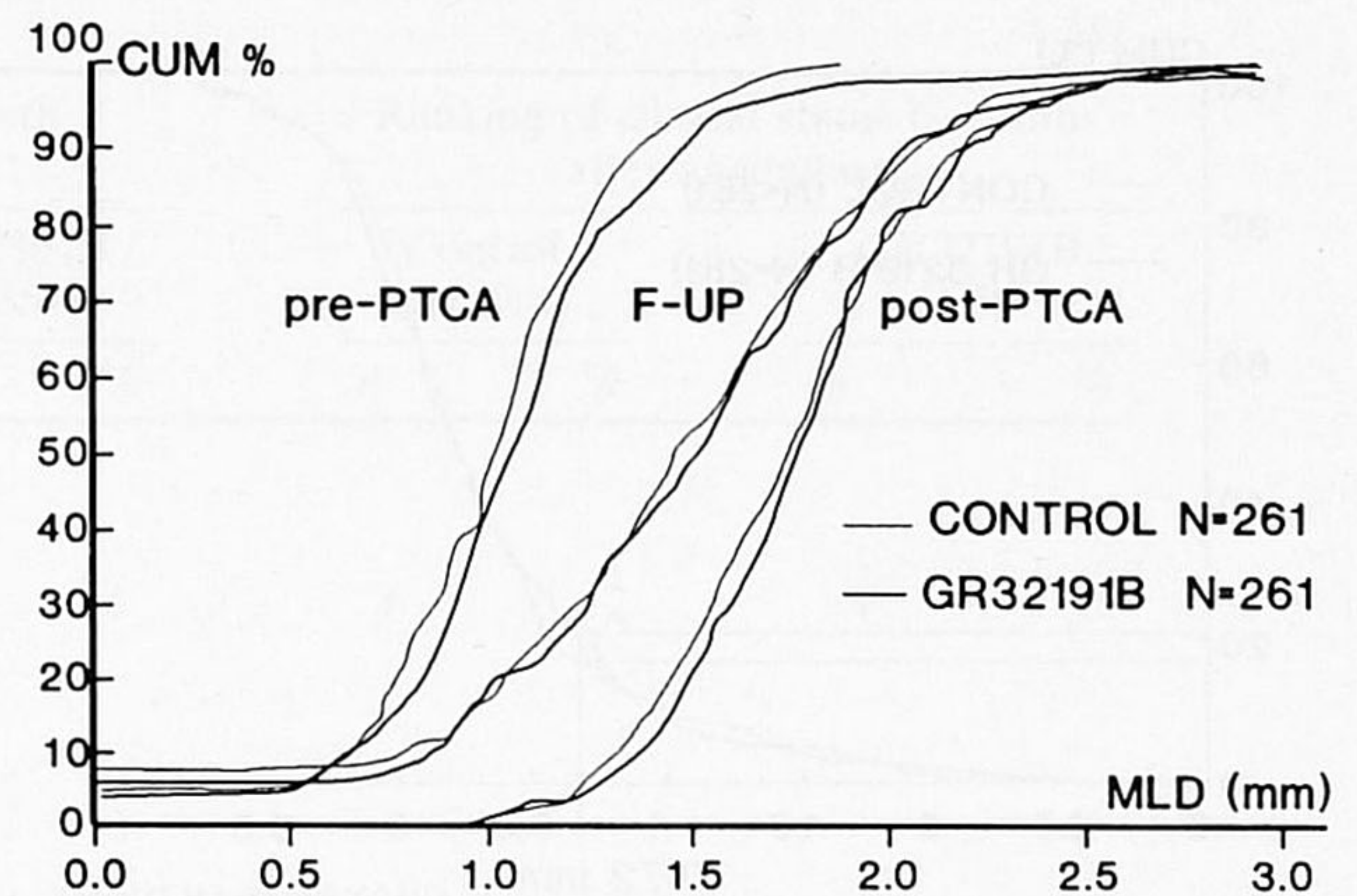


FIGURE 2. Cumulative distribution curve of minimal lumen diameter before percutaneous transluminal coronary angioplasty (PTCA), post-PTCA, and at 6-month follow-up (F-UP) in both treatment groups. CUM %, cumulative percentage of patients; MLD, minimal luminal diameter.

3 is a cumulative curve of the change in minimal lumen diameter observed in both groups. A loss of 0.72 mm or more^{5,27} corresponds to restenosis rates of 19% in the control group and 21% in the treated group. Therefore, the relative risk for restenosis in the treated group with respect to the control group is 1.15 (95% confidence intervals, 0.82, 1.60).

Results of Bicycle Ergometry

Of 649 patient who had a successful angioplasty, 539 underwent exercise testing at follow-up. Reasons for not performing the test were death (2 patients), unstable angina (45 patients), inability to perform the

TABLE 4. Quantitative Analysis of 636 Lesions in 522 Patients

	Control (n=261)	GR32191B (n=261)
Obstruction diameter (mm)		
Before angioplasty	0.99 ± 0.35	1.06 ± 0.39
After angioplasty	1.77 ± 0.34	1.79 ± 0.33
Follow-up	1.46 ± 0.59	1.49 ± 0.58
Reference diameter (mm)		
Before angioplasty	2.64 ± 0.57	2.70 ± 0.50
After angioplasty	2.71 ± 0.54	2.76 ± 0.48
Follow-up	2.72 ± 0.55	2.74 ± 0.52
Difference in obstruction diameter (mm)		
After angioplasty minus before angioplasty	0.78 ± 0.39	0.73 ± 0.38
Follow-up minus after angioplasty	-0.31 ± 0.54	-0.31 ± 0.55
Percentage stenosis (%)		
Before angioplasty	62 ± 13	61 ± 12
After angioplasty	34 ± 9	34 ± 9
Follow-up	46 ± 19	45 ± 19
Difference in percentage stenosis (%)		
After angioplasty minus before angioplasty	-28 ± 14	-26 ± 14
Follow-up minus after angioplasty	12 ± 20	11 ± 19

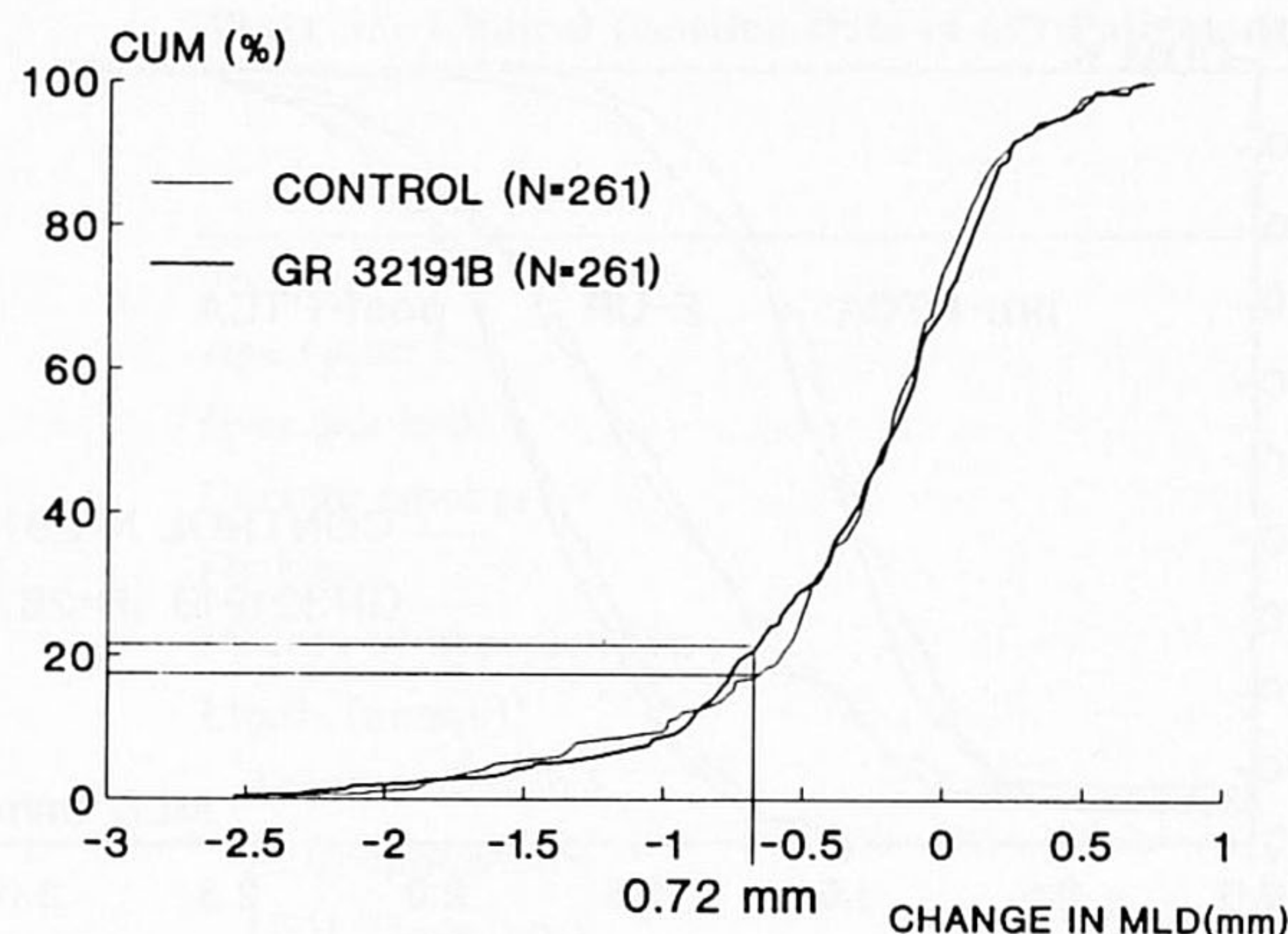


FIGURE 3. Cumulative distribution curve of change in minimal lumen diameter from after angioplasty to follow-up in both treatment groups. CUM %, cumulative percentage of patients; MLD, minimal luminal diameter.

test (19 patients), refusal (33 patients), and other (11 patients). Table 5 summarizes results of exercise testing in both groups. No difference in any parameter was observed at submaximal or maximal exercise. ST deviation (depression or elevation) of more than 0.1 mV (more than 1 mm) associated with anginal symptoms (considered positive) was observed in 47 patients in the control group and 55 patients in the GR32191B group.

Clinical Follow-up

Table 6 shows the total number of events during 6-month follow-up as well as the ranking of clinical status 6 months after angioplasty for all 697 patients randomized. Adjusted χ^2 test revealed no difference in ranking between the two groups. At 6-month follow-up, a comparable number of patients in both treatment groups were in each Canadian Cardiovascular Society class. Finally, 194 patients (56%) in the

treated group and 197 (56%) in the control group were event and symptom free at 6-month follow-up.

Results of GR32191B Assay and Platelet Aggregation Tests

In four of the six participating centers, GR32191B plasma levels for patients allocated to the GR32191B group were analyzed before first drug intake and approximately 1 hour after first drug dose. GR32191B was not detected above the limit of quantification in the predose samples but was present in the postdose samples at concentrations ranging from 5 to 1,210 ng/ml, with a mean of 392 ± 241 ng/ml, indicating that GR32191B was absorbed into the circulation after the oral administration of GR32191B.

During each follow-up visit of the Rotterdam patients, platelet aggregation tests were carried out using the TXA₂ mimetic U-46619 and ADP as aggregants. During the first three visits (3 weeks, 3 months, and 6 months after angioplasty), patients were on trial medication. The fourth visit (7 months after angioplasty) served as a control measurement. A total of 162 patients were tested at least one time during follow-up (Table 7). Mean ADP aggregation during visits 1, 2, and 3, expressed as peak response, was 116 ± 12 mm (214 analyses) in the treatment group and 125 ± 12 mm (203 analyses) in the control group (two-tailed *t* test, $p=0.4$). Mean U-46619 aggregation during visits 1, 2, and 3 was 10 ± 21 mm (215 analyses) in the treatment group and 100 ± 35 mm (203 analyses) in the control group (two-tailed *t* test, $p<0.0001$). This significant lowering of U-46619 aggregation in the treated group was observed in all except five patients during their 3-month test. These five patients showed U-46619 aggregation of more than 100 mm. At the 7-month assessment (patients off trial medication), mean U-46619 aggregation again rose to 80 ± 42 mm (27 analyses) in the treatment group, which is not significantly different from the value of 99 ± 32 mm (19 analyses) in the control group (two-tailed *t* test, $p=0.8$).

Bleeding Complications and Tolerability

Only mild bleeding events occurred in the trial. In-hospital bleeding events occurred in 18 patients (5%) in the control group and 15 patients (4%) in the treatment group (hematoma at puncture site of more than 5 cm, 14 versus 12 patients; prolonged bleeding at puncture site, three versus four; hematoma elsewhere, one versus none). During follow-up, four hematomas were reported in the control group and five in the treatment group. No cerebral bleeding or cerebral thrombotic events were encountered during the time course of the trial. Generally, the drug was well tolerated, and reported side effects were mild and evenly distributed in the two treatment groups. Total reported side effects were 40 in the control group and 44 in the treatment group (epigastric discomfort, 19 versus 20 patients; rash, 11 versus 12; nausea, six versus three; salivation, none versus two; headache, three versus six; fever, one versus one).

TABLE 5. Exercise Test Results

	Control (n=262)		GR32191B (n=277)	
	n	%	n	%
Position				
Supine	98	38	110	40
Sitting	164	62	167	60
ST deviation >0.1 mV	102	39	117	42
Anginal symptoms during test	76	32	73	30
Combination of >0.1 mV segment deviation and symptoms	47	18	55	20
Maximum work load (W)	142 ± 41		144 ± 40	
Expected work load (W)	160 ± 32		161 ± 39	
Exercise time (minutes)	7.8 ± 2.9		7.8 ± 3.0	
Systolic blood pressure at peak exercise (mm Hg)	193 ± 33		196 ± 31	
Heart rate at peak exercise (min ⁻¹)	133 ± 24		135 ± 22	

Test performed in 539 of 649 patients with successful angioplasty.

TABLE 6. Total Number of Events and Ranking Scale

	Total events during 6-month follow-up				Ranking of clinical status 6 months after angioplasty			
	Control (n=346)		GR32191B (n=351)		Control (n=346)		GR32191B (n=351)	
	n	%	n	%	n	%	n	%
Death								
Late	6		4					
All	6	2	4	1	6	2	4	1
Myocardial infarction								
Procedural	5		5					
Early	11		7					
Late	6		6					
All	22	6	18	5	22	6	18	5
Bypass graft surgery								
Procedural	3		7					
Early	5		2					
Late	18		18					
All	26	8	27	8	19	6	22	6
Repeat angioplasty								
Early	9		6					
Late	59		54					
All	68	20	60	17	52	15	49	14
CCS classification*								
IV	5	2	1	0.3	5	2	1	0.3
III	19	6	18	5	11	3	11	3
II	36	11	47	14	23	7	30	9
I	26	8	32	9	14	4	19	5
None	254	75	249	72	194	56	197	56

CCS, Canadian Cardiovascular Society angina classification. *For 687 patients alive at 6-month follow-up; secondary end point.

Discussion

Rationale for Selective Thromboxane Blockade in Prevention of Restenosis

At the time of the design of the trial in 1986, it was thought that platelet aggregation at the site of endothelial denudation and vascular disruption played a pivotal role in the pathogenesis of restenosis. Massive platelet deposition and aggregation at the dilatation site¹³ could, on the one hand, lead to organization of a mural thrombus²⁸ and, on the other hand, trigger a

fibroproliferative reaction of the vessel wall via the release of growth factors and chemotactic agents.

Balloon angioplasty causes a severe vascular trauma that can only be compared with spontaneous plaque rupture in unstable anginal syndromes,²⁹ with its known deleterious thrombotic consequences. Prevention of thrombotic events by blocking the TXA₂-induced aggregation with aspirin is known to be effective in unstable angina^{30,31} and in the periangioplasty period.^{32,33} Nevertheless, aspirin may still fall

TABLE 7. Platelet Aggregation Tests

Aggregation agent	Visit 1 (3 weeks)	Visit 2 (3 months)	Visit 3 (6 months)	Visit 4 (7 months)	Analysis of variance
ADP active (mm)	116±12	118±11	115±14	121±17	NS
n	81	72	61	26	
ADP control (mm)	124±13	126±11	127±11	118±11	p=0.03
n	81	69	53	19	
U46619 active (mm)	8±12	7±12	15±34	80±42	p<0.0001
n	81	72	62	27	
U46619 control (mm)	101±36	101±34	100±37	99±32	NS
n	81	69	53	19	

During visits 1, 2, and 3, patients were on trial medication.

short as the ideal agent because it is not sufficiently specific as an inhibitor of TXA₂ production.³⁴ Furthermore, by irreversibly acetylating cyclo-oxygenase and preventing the formation of the endoperoxide prostaglandin H₂, aspirin can block the production of "beneficial" prostaglandins such as prostacyclin as well as the "detrimental" TXA₂. A drug that preserved prostacyclin production while inhibiting the production or actions of TXA₂ might be expected to be superior to aspirin. This could be achieved either by a TXA₂ synthetase inhibitor or a TXA₂-receptor-blocking drug. However, no TXA₂ synthetase inhibitor is known to produce a complete blockage of TXA₂ synthesis. Furthermore, accumulating precursors of TXA₂, such as prostaglandin H₂, are also capable of inducing aggregation via the TXA₂-receptors.³⁵ In contrast, TXA₂-receptor blockade will antagonize not only the proaggregatory actions of TXA₂ but also those of agents that act indirectly via TXA₂, such as collagen, and agents that directly stimulate the TXA₂-receptor, such as prostaglandin H₂. A role for TXA₂-receptor blockade after PTCA has been suggested by an experimental animal model showing reduced intimal hyperplasia after balloon injury of rat carotids after treatment with GR32191 (M. Zimmerman, personal communication).

GR32191 (in doses of 0.125–1.0 mg/kg p.o.) produced a dose-related antagonism of U-46619-induced platelet aggregation *ex vivo*, which at the 1-mg/kg dose persisted for more than 24 hours.³⁶ GR32191B has also been demonstrated to produce a long-lasting blockade of the TXA₂-receptor on vascular smooth muscle *in vivo* in humans.³⁶ Chronic dosing (17.5 mg b.i.d.) resulted in progressively increasing antagonism of U-46619-induced aggregation such that virtually complete inhibition was achieved over the entire 12-hour dosing cycle.³⁷ In healthy volunteers³⁷ as well as in our patients, the drug was well tolerated, and bleeding time was only slightly prolonged. Finally, GR32191 is entirely devoid of any agonistic actions.³⁸

Trial Design

The design of CARPORT was based on four considerations, each of them having specific consequences. First, it was the underlying assumption that TXA₂-receptor blockade with GR32191B started before angioplasty would, at least in theory, affect both acute restenosis resulting from platelet aggregation-induced thrombus formation and chronic restenosis resulting from platelet aggregation-induced hyperplasia. Second, in view of the fact that patients in whom angioplasty did not succeed are not "at risk" for restenosis, trial medication was continued only in case PTCA was successful. Third, at this stage of the development of the therapeutic principle involved, it was considered necessary to establish the mechanism of action by direct observation of restenosis by angiography. As a consequence, the protocol included follow-up angiography regardless of clinical status. Within-patient change of minimal lumen diameter, as assessed by objective, quantitative measurements

of coronary segments filmed in multiple matched projections, was chosen as primary end point. Furthermore, the number of patients was planned based on what was known about the reproducibility of this method rather than on the need to have sufficient power for detecting an effect on clinical outcome (which would have required a much larger number of patients). Fourth, it was considered unethical not to give any protection against acute thrombotic events during angioplasty to participating patients.^{32,33} As a consequence, one dose of intravenous aspirin was given before PTCA to the control group before placebo was started.

Loss in Minimal Luminal Diameter as Primary End Point: A Noncategorical Approach

The reappearance of angina as a sole criterion of restenosis underestimates the angiographic rate of restenosis, and the value of recurrent anginal symptoms as a marker of restenosis is difficult to assess in many studies because the timing and completeness of angiographic follow-up often have been determined by symptomatic status.³⁹

In the present trial, repeat catheterization with quantitative angiography was obtained in 88.5% of 649 patients with a successful angioplasty. A majority of patients (354 of 522, or 68%) were recatheterized in the 6-month (± 2 weeks) time interval. The remaining patients underwent early recatheterization because of clinical suspicion for restenosis. Of the 522 compliant patients who had angiography at follow-up, 345 were angina free and 165 were symptomatic at follow-up. As shown in Figure 4B, there was considerable overlap between the change in minimal lumen diameter of patients with and of those without angina at follow-up angiography. This underscores that reappearance of angina is a poor proxy to the anatomic substrate at issue and confirms the poor predictive value of symptoms found in other studies,³⁹ which may be explained by the presence of other mechanisms for angina, such as incomplete revascularization or progression of disease in other vessels.

Several studies have examined the usefulness of ergometry to detect restenosis after angioplasty.³⁹ These studies have generally found that the presence of exercise-induced angina, ST segment depression, or both is not highly predictive of restenosis whether the test is performed early or late after angioplasty.³⁹ Figure 4B illustrates this for our data in a similar fashion as for angina. In view of the above, quantitative coronary angiography has emerged as the most reliable method for judging late results.

In studies evaluating the biology of restenosis, a continuous measure of the degree of lumen obstruction is preferable because any progression of the stenosis reflects the process of interest regardless of whether an arbitrarily defined threshold of obstruction is reached. Keeping in mind that an angiographic restenosis study assesses only the anatomic component of the restenosis problem, there is no

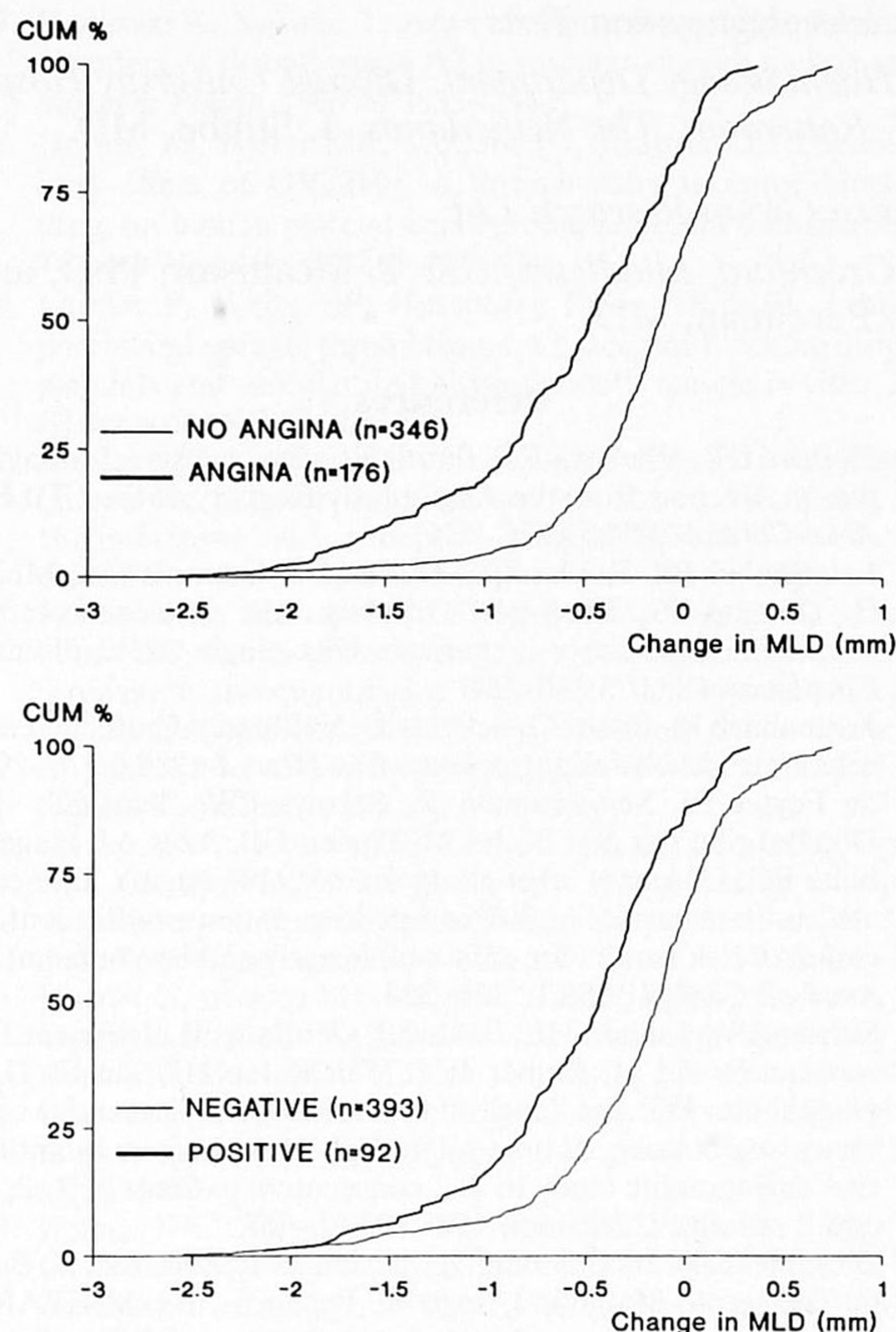


FIGURE 4. Top panel: Cumulative distribution (CUM %) curve of change in minimal lumen diameter (MLD) for symptomatic and asymptomatic patients at follow-up angiography. Bottom panel: Cumulative distribution (CUM %) curve of change in minimal lumen diameter (MLD) for patients with positive ergometry and negative ergometry at follow-up angiography.

threshold above which a loss of lumen diameter would have clinically significant functional or symptomatic consequences. Why, then, would one try to define a threshold above which there would be "significant" quantitatively determined angiographic restenosis? To define the threshold on consideration of reproducibility of the measurement in individual patients is also questionable. The expected benefit of a treatment can be measured with much greater precision by using the change in lumen diameter for the group. If it is assumed that treatment reduces the loss of lumen diameter from 0.4 mm under control conditions to 0.25 mm under active medication, 233 patients per treatment group are required for there to be a power of 90%. The above reduction corresponds with restenosis rates (defined as a loss of minimal lumen diameter of 0.72 mm or more) of 25% and 17.5%, respectively.^{5,27} This difference, however, can be statistically detected only with 620 patients per treatment group (power, 90%). Thus, statistically, the quantitative outcome determined from direct measurements of continuous variables can be evaluated with only one third of the number of

patients required for the categorical outcome. This is logical because categorical end points do not take full advantage of the available information.

Possible Explanations for Lack of Effect of GR32191B

In this trial, TXA₂-receptor blockade failed to demonstrate prevention of angiographic restenosis after angioplasty. Also, there was no apparent effect on overall clinical outcome. There are several possible explanations.

First, it could be hypothesized that the absence of benefit was due to poor absorption. In four participating clinics, plasma levels of GR32191B before first drug dose and 1 hour afterward confirmed an excellent gastrointestinal resorption of the drug in this group of patients with coronary artery disease who were fasting while awaiting an angioplasty procedure. Second, compliance could have been poor. Aggregation tests in one participating clinic showed that a 90% reduction of platelet aggregation via the TXA₂ pathway was achieved in the treated group throughout the entire study. This indicated that patients were taking their medication and that the drug was pharmacologically active. Third, it might be hypothesized that this substantial reduction in the aggregatory response of the platelet is still insufficient to prevent a substantial release of other factors involved in the initiation of the proliferative response.^{13,40-42} In a recently published study, it was shown that GR32191 had no effect on primary aggregation induced by ADP, adrenaline, or platelet aggregating factor.⁴³ In the present study, GR32191 was found to inhibit only 70% of the total platelet deposition on deendothelialized rabbit aorta using ¹¹¹In-labeled human platelets from whole blood.⁴³ This was similar to the maximum inhibition achieved with prostacyclin and aspirin. Because several clinical trials with aspirin after balloon angioplasty have failed to prove a beneficial effect on restenosis,^{32,44-46} it might be retrospectively inferred that a similar level of platelet inhibition would also fail to alter the restenosis rate. Furthermore, the magnitude of TXA₂-receptor blockade needed after balloon-induced vascular damage is not known. For example, a substantial increase in plasma levels of TXA₂ metabolite 11-dehydro-thromboxane B₂ from less than 50 to 174 pg/ml has been measured in the great cardiac vein after angioplasty of the left anterior descending coronary artery, despite pretreatment with aspirin.⁴⁷ One could question whether TXA₂-receptor blockade is effective in the face of such an increase, although it has been demonstrated that GR32191 can achieve a more-than-100-fold displacement to the right of the platelet aggregation concentration-effect curve for U-46619 in healthy subjects.³⁶

More recently, it has been advocated that inhibition of platelet adhesion is a more efficient means to prevent subsequent aggregation of platelets.⁴⁸⁻⁵¹ However, it can be argued that complete inhibition of adhesion will cause untoward bleeding effects.

Finally, the pivotal role of the platelet in the initiation of the restenosis process might have been overestimated,⁵² and antiplatelet therapy as the sole modality of treatment may be intrinsically insufficient to control the restenosis phenomenon.

Appendix

CARPORT Study Group

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