

# Evaluation of Ketanserin in the Prevention of Restenosis After Percutaneous Transluminal Coronary Angioplasty

## A Multicenter Randomized Double-Blind Placebo-Controlled Trial

P.W. Serruys, MD, PhD; W. Klein, MD; J.P.G. Tijssen, PhD; W. Rutsch, MD; G.R. Heyndrickx, MD, PhD; H. Emanuelsson, MD, PhD; S.G. Ball, MD; O. Decoster, MD; E. Schroeder, MD; H. Liberman, MD; E. Eichhorn, MD; J.T. Willerson, MD; H.V. Anderson, MD; F. Khaja, MD; R.W. Alexander, MD; D. Baim, MD; R. Melkert, MD; J.C. van Oene, PhD; R. Van Gool, MD, MPH

**Background.** Ketanserin is a serotonin  $S_2$ -receptor antagonist that inhibits the platelet activation and vasoconstriction induced by serotonin and also inhibits the mitogenic effect of serotonin on vascular smooth muscle cells.

**Methods and Results.** We conducted a randomized, double blind, placebo-controlled trial to assess the effect of ketanserin in restenosis prevention after percutaneous transluminal coronary angioplasty (PTCA). Patients received either ketanserin (loading dose, 40 mg 1 hour before PTCA; maintenance dose, 40 mg bid for 6 months) or matched placebo. In addition, all patients received aspirin for 6 months. Coronary angiograms before PTCA, after PTCA, and at 6 months were quantitatively analyzed. Six hundred fifty-eight patients were entered into the intention-to-treat analysis. The primary clinical end point of the study was the occurrence between PTCA and 6 months of any one of the following: cardiac death, myocardial infarction, the need for repeat angioplasty, or bypass surgery. It also included the need for revascularization actuated by findings at 6-month follow-up angiography. The primary clinical end point was reached by 92 (28%) patients in the ketanserin group and 104 (32%) in the placebo group (RR, 0.89; 95% CI, 0.70, 1.13;  $P=.38$ ). Quantitative angiography after PTCA and at follow-up was available in 592 patients (ketanserin, 287; control, 305). The mean difference in minimal lumen diameter between post-PTCA and follow-up angiogram (primary angiographic end point) was  $0.27 \pm 0.49$  mm in the ketanserin group and  $0.24 \pm 0.52$  mm in the control group (difference, 0.03 mm; 95% CI,  $-0.05, 0.11$ ;  $P=.50$ ).

**Conclusions.** Ketanserin at the dose administered in this trial failed to reduce the loss in minimal lumen diameter during follow-up after PTCA and did not significantly improve the clinical outcome. (*Circulation*. 1993;88[part 1]:1588-1601.)

**KEY WORDS** • ketanserin • restenosis • angioplasty

**P**ercutaneous transluminal coronary angioplasty (PTCA) is increasingly used to alleviate coronary artery stenosis and its ischemic repercussions. Despite an upgrading of technology, the technique remains limited by restenosis of the dilated segment in 25% to 35% of cases; this occurs mainly within 4 to 6 months after PTCA.<sup>1</sup> In the early phase after PTCA, restenosis is mainly due to thrombosis.<sup>2,3</sup> Later on, vascular smooth muscle cell proliferation and synthetic activity result in pronounced intimal thickening and play a major role in renarrowing the lumen of the dilated vessels.<sup>4-7</sup> These phenomena leading to restenosis are initiated by endothelial denudation and intimal and medial damage. This first gives rise to adhesion and subsequently to accumulation of activated

platelets on the vascular lesion,<sup>4,8-10</sup> which results in the release of various platelet-derived products, including platelet-derived growth factor (PDGF), 5-hydroxytryptamine (5-HT), prostaglandin endoperoxides, thromboxane  $A_2$ , and adenosine diphosphate (ADP).<sup>11-14</sup> Platelet-derived prostanoids, ADP, 5-HT, and thrombin are primarily involved in the platelet-dependent genesis of occluding arterial thrombi and of vasospasms in areas with deficient endothelium-dependent relaxation,<sup>11,15-18</sup> while PDGF in particular as a potent mitogen for vascular smooth muscle cells in vitro<sup>19,20</sup> has been implicated in intimal hyperplasia in reaction to vessel wall damage.<sup>20,21</sup> However, platelet-derived 5-HT also stimulates migration and proliferation of vascular smooth muscle cells<sup>19,22-25</sup> and promotes the synthesis of collagen and proteoglycans by isolated cells.<sup>24,26,27</sup> The 5-HT-induced stimulation of platelet aggregation as well as stimulation of vascular smooth muscle cell proliferation appear to be mediated by the 5-HT<sub>2</sub>

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Correspondence to Dr Serruys, Catheterization Laboratory, Thoraxcenter, Postbox 1738, 3000 DR Rotterdam, The Netherlands.



serotonin receptor subtype, since these effects were blocked by the selective 5-HT<sub>2</sub> antagonist ketanserin. In a small placebo-controlled study, Klein et al<sup>28</sup> found that intravenous infusion with ketanserin added to acetyl salicylic acid, heparin, and a calcium antagonist appeared to reduce the incidence of occlusion or early reduction of diameter 24 hours after angioplasty.

The present study, referred to as the Post-Angioplasty Restenosis Ketanserin (PARK) Study, was carried out to further evaluate the role of ketanserin in the prevention of restenosis and its clinical complications after PTCA.

## Methods

### Study Population

Consecutive patients with symptoms of stable or unstable angina pectoris due to single or multivessel coronary artery disease, who were scheduled to undergo elective PTCA, were considered for inclusion. A total of 5636 patients were screened, of whom 4932 were excluded from the trial because of the criteria listed in Table 1.

### Treatment Allocation

The trial was carried out in accordance with the declaration of Helsinki (1973) and its revision in Venice (1983) in 15 participating centers. Written informed consent was obtained from 704 patients who met the selection criteria. Once included, these patients were randomized to double-blind treatment with either ketanserin (maintenance dose, one 40-mg tablet twice daily) or matching placebo. Treatment with oral trial medication was continued until repeat angioplasty at 6 months after the original PTCA. Trial medication was always started at least 1 hour before balloon insertion.

In the first 79 patients, trial medication at the start consisted of an intravenous bolus injection of ketanserin (10 mg given over 3 minutes) followed by an intravenous infusion of 4 mg/h. The application of intravenous trial medication was continued until 1 hour after the last balloon inflation. Patients randomized to placebo received the corresponding solvent volumes in a double-blind fashion. In the subsequent 625 patients, trial medication at the start consisted of an oral tablet (40 mg ketanserin or matching placebo). In all patients, the application of trial medication was resumed 3 to 10 hours after the last balloon inflation with an oral tablet (40 mg ketanserin or placebo). As a mandatory concomitant therapy, acetylsalicylic acid (250 to 500 mg per 24 hours) was started at least 1 hour before balloon insertion and was also continued until follow-up angiography at 6 months. Heparin 10 000 IU was given for the first hour of the procedure to be followed by supplementary heparin at the discretion of the treating physician. When calcium antagonists were already being taken before randomization, they could be continued. Potassium-losing diuretics were only allowed to be taken in combination with potassium-sparing diuretics, such as amiloride or triamterene. Antiplatelet drugs, including nonsteroidal anti-inflammatory drugs other than acetylsalicylic acid and anticoagulants, were not allowed. Trial medications were packed and supplied by the Janssen Research Foundation, which also prepared

**TABLE 1. Reasons for Exclusion for 3437 of 3902 Screened Patients in 10 of 14 Participating Centers**

Previous angioplasty of the same vessel or branches thereof	541 (16%)
Large myocardial infarction within the last 2 weeks (max CK >5×normal)	291 (8%)
Factors making follow-up difficult (no fixed address, etc)	258 (7%)
Participation in another study with any investigational drug (<30 days)	246 (4%)
Informed consent refused	184 (5%)
Use of potassium losing diuretics or hypokalemia (K≤3.5 mmol/L)	168 (5%)
Intended angioplasty of a coronary bypass	155 (5%)
Factors making repeat angiography unlikely	139 (4%)
Intended surgical interventions	41 (1%)
Evolving myocardial infarction (at present CK >2×normal)	35 (1%)
Previous participation in this study	32 (1%)
Indication for (continued) treatment with oral anticoagulants	30 (1%)
Contraindication for treatment with acetyl salicylic acid	28 (1%)
Women who were potentially childbearing	25 (1%)
Contraindication to discontinue preexisting treatment with an antithrombotic agent	24 (1%)
Life expectancy less than 1 year	23 (1%)
Indication for (continued) use of a class Ia, Ic, or III antiarrhythmic drug	17 (<1%)
Documented peptic ulcer or upper gastrointestinal bleeding (<6 months)	15 (<1%)
History of bleeding disorder	11 (<1%)
Severe hepatic disease	10 (<1%)
QT interval exceeding 500 milliseconds in the resting ECG	9 (<1%)
Cerebrovascular accident(s) (<6 months)	4 (<1%)
Under 30 years of age	3 (<1%)
Second- or third-degree heart block	3 (<1%)
Other	1079 (31%)

the randomized plan of drug administration. Randomization was stratified by center.

### Angioplasty Procedure and Follow-up Angiography

The angioplasty procedures were left to the discretion of the operator. Multistage procedures (dilations of different sites during separate procedures) were considered one procedure as long as they took place within 1 week.

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 after discontinuation of the trial medication. 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 3 months, the patient was asked to undergo another coronary angiogram at 6 months. To achieve maximal vasodilatation, each angiogram was preceded by either nitroglycerin or isosorbide dinitrate given intracoronarily. 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 per second. 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 post-angioplasty 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 post-angioplasty and follow-up angiograms, measures were undertaken as has been described earlier.<sup>29-31</sup> The analyses were performed at the core laboratory; the personnel were blinded to treatment allocation and did not have access to clinical data.

The accuracy and precision of the edge detection procedure of the CAAS system as assessed from cinefilm of contrast-filled acrylate models are  $-30$  and  $90$   $\mu\text{m}$ , respectively; the variability of the analysis procedure itself in terms of absolute lumen dimension is less than  $0.12$  mm. The short-, medium- and long-term measurement variability has been assessed from repeated coronary angiographic examination performed 5 minutes, 1 hour, and 90 days apart, respectively. For all studies, the mean difference in absolute diameter was less than  $0.13$  mm.<sup>32</sup> Since one of the main criticisms of angiography has been the potential measurement inaccuracy and imprecision immediately after balloon angioplasty when disruption of vessel contour is virtually always produced, we have recently analyzed the change in minimal lumen diameter (MLD) observed over a period of 24 hours after PTCA. Post-PTCA accuracy and precision of MLD measurement by the CAAS system are  $\pm 0.1$  mm and  $\pm 0.2$  mm, which are eminently acceptable.<sup>33</sup>

The morphology of the stenotic lesions was analyzed and reported according to the Ambrose classification.<sup>34</sup> The TIMI perfusion index was determined by the core laboratory, and the incidence of TIMI 0 and TIMI 1 was reported. The percentages of the stenotic lesions from which a side branch originated are tabulated in Table 2, as well as the number of lesions in which the origin of side branch was involved during balloon inflation. A stenosis was considered to be located in a bend, if, in any nonforeshortened angiographic projection, it appeared that the balloon in position for the dilatation was located in a portion of the vessel that was angulated more than  $45^\circ$  in diastole.<sup>35</sup>

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.

All postangioplasty angiograms were examined for the presence or absence of dissection—defined according to modified National Heart, Lung, and Blood Insti-

tute criteria—as the presence of angiographically evident intimal or medial damage, presenting either as a small radiolucent area within the lumen of the vessel (tear or flap, type A) or as an extravasation of nonpersisting or persisting contrast medium (type B or C).<sup>36</sup> A dissection was classified as type D in the presence of a spiral-shaped filling defect with delayed distal flow and as type E if a persistent luminal defect with delayed antegrade flow was seen on the final post-coronary angioplasty angiogram. A filling defect accompanied by a total coronary occlusion was classified as a type F dissection.

The absolute values of the MLD and the reference diameter (both in millimeters) were measured using the contrast-empty catheter diameter as a scaling device. In case of total occlusion or lesion with TIMI-1 perfusion, a value of  $0$  mm was used for the MLD and  $100\%$  was used for the percent diameter stenosis. In these cases, the post-PTCA reference diameter was used as the reference diameter pre-PTCA or at follow-up.

### *Clinical Follow-up*

Patients were seen in the outpatient clinic after 1 and 6 months for an interview, a physical examination, a tablet count, and an ECG. At 2 and 4 months, a telephone interview was performed for recording of clinical events and use of trial and concomitant medication. Clinical follow-up status was assessed at 6 months after the procedure either at repeat angiography or at a visit to the outpatient clinic. If this was not possible, the patient was interviewed by telephone. Plasma levels of ketanserin were determined before discharge as well as at 6 months.

### *End Points*

The primary clinical end point of the study was the occurrence of any one of the following: cardiac death, myocardial infarction, or the need for repeat angioplasty or bypass surgery (of the previously dilated sites) between the first balloon inflation and repeat angiography at 6 months (or 6 months calendar time if 6 months repeat angiography was not performed). This combined end point included periprocedural infarctions and emergency bypass surgery. An indication to perform repeat angioplasty or bypass surgery based on findings at 6-month repeat angiography constituted an end point provided that the treating physician could substantiate the decision on the basis of findings at angiography in combination with chest pain and/or electrocardiographic or scintigraphic evidence of myocardial ischemia either at rest or during exercise. Patients in whom no balloon inflation had occurred were left out of the analyses of the clinical end point ( $n=42$ ). All events that were potential end points were centrally reviewed. End point definitions were as follows: (1) cardiac death: all deaths were considered cardiac unless an unequivocal noncardiac cause could be established; (2) myocardial infarction: the presence of at least two of the following: (a) occlusion of a previously patent coronary artery, (b) prolonged chest pain, (c) a serial enzyme pattern typical of myocardial infarction with at least one cardiac enzyme raised to more than twice the local upper limit for normal, and (d) the development of new Q wave formation; (3) repeat angioplasty: repeat angioplasty after the initial procedure involving at least one of the



**TABLE 2. Angiographic Baseline Data of Patients in Intention-to-Treat Analysis**

	Ketanserin (N=328)	Placebo (N=330)
No. of lesions	409	407
No. of lesions per patient	1.25	1.23
<b>Description of lesions before angioplasty</b>		
Location of lesion		
RCA	114 (28)	140 (34)
LAD	189 (46)	159 (39)
LCx	103 (25)	98 (24)
LM	1 (<1)	0 (<1)
Type of lesion <sup>29</sup>		
Concentric	170 (42)	179 (44)
Eccentric type IA	31 (8)	26 (6)
Eccentric type IB	81 (20)	77 (19)
Eccentric type IIA	11 (3)	15 (4)
Eccentric type IIB	14 (3)	16 (4)
Multiple irregularities	38 (9)	37 (9)
Tandem lesion	15 (4)	16 (4)
TIMI 0	24 (6)	17 (4)
TIMI I	20 (5)	21 (5)
Side branch in stenosis	155 (38)	160 (40)
Side branch in dilatation site	275 (68)	288 (71)
Relationship to artery bend	103 (25)	110 (27)
Vessel calcified	57 (14)	48 (12)
<b>PTCA procedure</b>		
Total duration of inflation (s)	227±177	229±238
Nominal size of the largest balloon (mm)	2.86±0.42	2.84±0.41
Max inflation pressure (atm)	8.86±2.70	9.00±6.21
Balloon to artery ratio	1.13±0.18	1.10±0.17
<b>Visual assessment of PTCA result</b>		
Grade of perfusion (TIMI score)		
TIMI 0	4 (1)	4 (1)
TIMI I	2 (<1)	3 (1)
TIMI II	8 (2)	14 (3)
TIMI III	388 (96)	385 (95)
Not applicable	1 (<1)	0 (0)
Dissection at the dilated site <sup>31</sup>		
No dissection	276 (68)	251 (62)
Type A	51 (13)	66 (16)
Type B	56 (14)	63 (16)
Type C	17 (4)	16 (4)
Type D	2 (<1)	1 (<1)
Type E	2 (<1)	3 (1)
Type F	2 (<1)	2 (<1)
Thrombus visible		
Before PTCA	14 (3)	12 (3)
After PTCA	16 (4)	6 (1)
Before and after PTCA	2 (<1)	10 (2)

RCA indicates right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LM, left main stem; TIMI, Thrombosis in Myocardial Infarction; and PTCA, percutaneous transluminal coronary angioplasty.



previously dilated lesions; (4) and bypass surgery: emergency bypass surgery or elective coronary bypass surgery involving at least one of the previously dilated lesions (coronary bypass involving other coronary arteries only did not constitute an end point).

The primary angiographic end point of the study was the within-patient change in MLD at the dilated coronary site(s) at follow-up relative to post-PTCA. If a revascularization procedure involving the dilated lesion had been performed before 6-month repeat angiography, the last angiogram obtained before the intervention, if available, was used. In the absence of a 6-month repeat angiogram, the last angiogram obtained within the previous 3 months, if available, was used, provided that no end points had taken place.

For each dilated segment, the MLD was taken as the mean value from multiple matched projections ( $2.2 \pm 0.7$  per lesion and orthogonal whenever possible). Within-patient change was defined as the follow-up minus the post-PTCA value. In case more than one segment was dilated (multivessel or multisite procedures), the mean change of all lesions was taken as the angiographic end point.

Secondary end points of the study were: (1) the change in percentage diameter stenosis ( $100\% \times [\text{reference diameter minus MLD}] / \text{reference diameter}$ ) at the dilated site(s) at follow-up angiography relative to baseline, (2) evidence of restenosis at follow-up angiography indicated by a change from  $<50\%$  stenosis post-PTCA to  $>50\%$  at follow-up, and (3) the clinical status of each patient at the end of follow-up ranked according to the following ordinal scale (definitions as above): 1, death; 2, myocardial infarction; 3, coronary artery bypass graft (CABG); 4, repeat PTCA; 5, presence of angina pectoris, either exertional (Canadian Cardiovascular Society [CCS] classification 1 or higher) or nonexertional; and 6, none of the above.

### Analysis

The main clinical analysis consisted of a single comparison between the trial medication groups of the primary clinical end point, irrespective of the time of its occurrence, involving all randomized patients with the exception of those in whom no balloon inflation had taken place (intention-to-treat analysis). The main analysis of the angiographic data was a comparison of change in lumen diameter from post-PTCA to late follow-up (loss) in patients treated with ketanserin to those treated with placebo, involving all patients of the main clinical analysis with analyzable angiograms (angiographic efficacy analysis). In addition, the primary angiographic end point was analyzed involving those patients who had been compliant until the time of follow-up angiography (per protocol analysis). A patient was judged compliant if at least 80% of the trial medication had been taken and this medication had not been interrupted for more than 14 consecutive days.

An unpaired *t* test was used for the angiographic and other continuous variables, and a  $\chi^2$  test was used for event rates and other discrete factors.<sup>37</sup> Whenever possible, estimates of the magnitude of the trial medication effect (ketanserin relative to placebo) with corresponding 95% confidence intervals are provided. Relative risks are in all cases given as ketanserin relative to placebo.

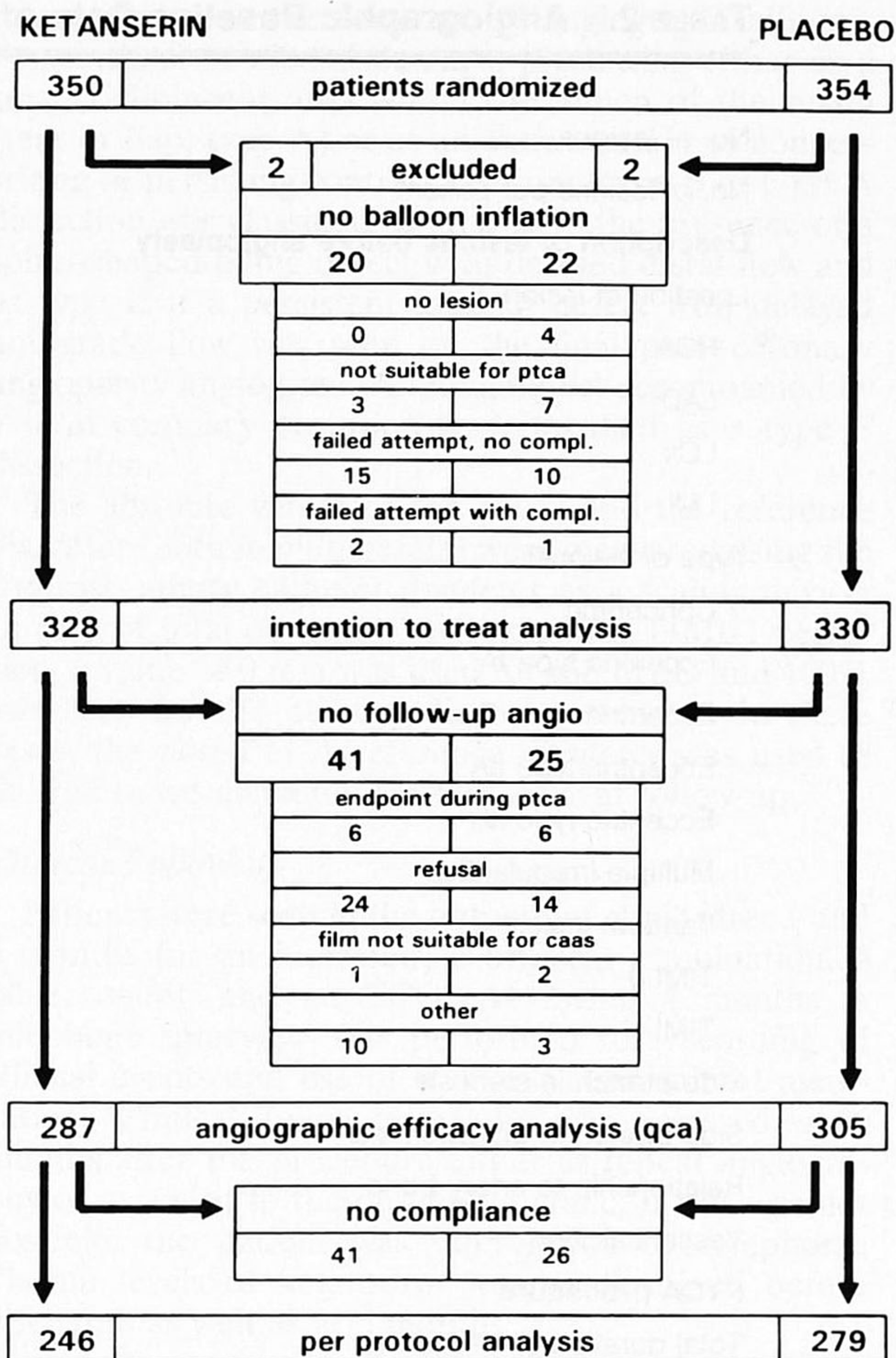


FIG 1. Patient flowchart in the PARK trial. *ptca* indicates percutaneous transluminal coronary angioplasty; *compl*, complication; and *qca*, quantitative coronary angiography.

## Results

### Patient and Baseline Characteristics

Fig 1 shows the patient flowchart. Seven hundred four patients were randomized. Four patients (ketanserin, 2; placebo, 2) were included inappropriately and 42 patients (ketanserin, 20; placebo, 22) did not undergo balloon inflation. The intention-to-treat analysis therefore comprised 658 patients.

Quantitative angiographic follow-up was not available in 66 patients (ketanserin, 41; placebo, 25) for various reasons. The angiographic efficacy analysis thus comprised 592 patients. Finally, 67 patients (ketanserin, 41; placebo, 26) did not fulfill the compliance criteria and were excluded from the per protocol analysis, which thus comprised 525 patients.

Selected demographic and clinical characteristics of the two study groups are shown in Tables 2 and 3. Table 4 shows the clinical events that occurred. Clinical follow-up was obtained for all 658 patients, except for one patient, who was lost to follow-up after the 2-month telephone interview (moved abroad), when no event had occurred.

### Clinical End Points

The primary clinical end point occurred in 92 of 328 ketanserin patients and in 104 of 330 placebo patients.



**TABLE 3. Clinical Baseline Data of 658 Patients Included in Analysis for Clinical End Points**

	Ketanserin (N=328)	Placebo (N=330)
<b>Age (y)</b>		
30-50	79 (24)	87 (26)
51-60	127 (39)	126 (38)
>60	122 (37)	117 (35)
<b>Male sex</b>	263 (80)	264 (80)
<b>Smoking status</b>		
Current	61 (19)	64 (19)
Previous	164 (50)	165 (50)
Never	103 (31)	101 (31)
<b>Diabetes mellitus</b>	38 (12)	36 (11)
<b>Previous myocardial infarction</b>	131 (40)	129 (39)
<b>Previous CABG</b>	15 (5)	13 (4)
<b>Previous PTCA</b>	10 (3)	16 (5)
<b>History of hypertension</b>	103 (31)	131 (40)
<b>History of hypercholesterolemia</b>	132 (40)	156 (47)
<b>History of stroke</b>	8 (2)	8 (2)
<b>History of peripheral vascular disease</b>	22 (7)	25 (8)
<b>Exertional angina</b>		
CCS class I	46 (14)	46 (14)
CCS class II	124 (38)	131 (40)
CCS class III	105 (32)	103 (31)
CCS class IV	31 (9)	27 (8)
No exertional angina	22 (7)	23 (7)
<b>Nonexertional angina</b>	132 (40)	153 (46)
<b>Medication at screening</b>		
Nitrates	173 (53)	183 (55)
Ca antagonists	204 (62)	223 (68)
$\beta$ -blockers	186 (57)	187 (57)
Monotherapy	108 (33)	96 (29)
Double therapy	127 (39)	154 (47)
Triple therapy	67 (20)	63 (19)
No therapy	26 (8)	17 (5)

CABG indicates coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; and CCS, Canadian Cardiovascular Society angina classification. Numbers in parentheses are percentages.

The relative risk for the ketanserin group to the placebo group was 0.89, with a 95% confidence interval ranging from 0.70 to 1.13. Fig 2 shows the cumulative distributions of the primary clinical end point over time for both treatment groups. The two curves are not strictly superimposed, indicating that throughout the trial there was a slightly lower cumulative incidence of clinical end points in the group treated with ketanserin as compared with the placebo group.

During the course of the study, 4 patients died (ketanserin, 2; placebo, 2). The cause of death was in all cases cardiovascular (ketanserin: death after 3 months

in connection with CABG after various unsuccessful angioplasty procedures; death after an unsuccessful initial procedure and patient refusal of further treatment; placebo: death after 2 weeks due to severe neurological damage after complicated initial PTCA and emergency CABG; and death after 3 months after myocardial infarction due to thrombosis of stent). Non-fatal myocardial infarction was documented in 24 patients (ketanserin, 13; placebo, 11); 49 patients underwent bypass surgery (ketanserin, 21, placebo, 28); and 145 patients underwent repeat PTCA, atherectomy, laser angioplasty, or stent implantation (ketanserin, 69; placebo, 76). At 6-month follow-up, a comparable number of patients in both treatment groups were in each CCS class. Recurrent angina was observed in 242 patients (ketanserin, 111; placebo, 131). Finally, 181 patients (54%) in the ketanserin group and 176 (51%) in the placebo group were event and symptom free at 6-month follow-up.

There were more patients with adverse experiences in the ketanserin group (220 of 328) than in the placebo group (173 of 330). The most frequently reported adverse experiences are summarized in Table 5. Complaints of dizziness and dry mouth appeared to be more common in the ketanserin group than in the placebo group, as was the occurrence of hypotensive episodes. Such adverse experiences could be expected from the known side-effect profile of ketanserin, a compound used for the treatment of hypertension at daily doses of 20 mg bid.<sup>38</sup>

#### *Result of the Angiographic Analysis (Angiographic Efficacy Analysis)*

Table 6 summarizes the quantitative angiographic findings in the angiographic efficacy analysis. The loss at follow-up in MLD was  $0.27 \pm 0.49$  mm in the ketanserin group and  $0.24 \pm 0.52$  mm in the control group (treatment effect, 0.03 mm; 95% confidence interval, -0.05 to 0.11 mm). Figs 3 and 4 represent cumulative frequency curves of the MLD and of the loss in MLD observed in both groups.

The restenosis rate per lesion according to the >50% diameter stenosis criterion is 32% in the ketanserin group and 32% in the placebo group, with a relative risk of 0.99 (95% confidence interval, 0.78, 1.25).

### **Discussion**

#### *Rationale for Serotonin Antagonism in the Prevention of Restenosis*

Ketanserin is a serotonin 5HT<sub>2</sub>-receptor antagonist. It inhibits serotonin-induced platelet activation and vasoconstriction, but it does not inhibit serotonin-induced vasodilation.<sup>39</sup> In case of damaged endothelium, however, serotonin gains direct access to the smooth muscle cells, causing them to contract.<sup>40</sup> Serotonin is an important mediator in cyclic flow reduction in stenotic and injured arteries.<sup>41</sup> This phenomenon was associated with abundant intimal hyperplasia in the 3 weeks after intimal denudation in animals.<sup>12,42</sup> It was thus surmised that prevention of this phenomenon would directly or indirectly prevent an exuberant wound healing process and the active intimal hyperplasia after wall injury.

Serotonin is released from the dense granules of aggregating platelets. In itself, it is a weak agonist for



**TABLE 4. Occurrence During 6-Month Follow-up of Clinical Events and the Primary Clinical End Point**

	Ketanserin (N=328)	Placebo (N=330)	RR (95% CI)
<b>Death</b>			
After initial PTCA, before discharge	1	1	
After discharge	1	1	
All	2 (<1%)	2 (<1%)	1.01 (0.14-7.10)
<b>Myocardial infarction</b>			
During initial PTCA	1	3	
After initial PTCA, before discharge	6	4	
After discharge	6	4	
All	13 (4%)	11 (3%)	1.19 (0.54-2.62)
<b>CABG</b>			
Periprocedural	5	6	
After initial PTCA, before discharge	3	6	
<6 mo	9	12	
>6 mo	4	4	
All	21 (6%)	28 (8%)	0.75 (0.44-1.30)
<b>Repeat angioplasty</b>			
Within 1 wk	5	9	
<6 mo	27	28	
>6 mo	37	39	
All	69 (21%)	76 (23%)	0.91 (0.68-1.22)
<b>Primary clinical end point*</b>	<b>92 (28%)</b>	<b>104 (32%)</b>	<b>0.89 (0.70-1.13)</b>

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

Numbers are patients who experienced at least one of the respective events; <6 mo indicates after 1 week/discharge, before 6-month repeat angiography; >6 mo, subsequent to 6-month repeat angiography.

\*See text.

platelet activation, but it enhances the activity of other platelet agonists, such as ADP, thromboxane A<sub>2</sub>, catecholamines, and thrombin, by a positive feedback loop. The *in vitro* evidence with human platelets suggests that serotonin can substantially contribute to strong platelet activation through amplification, a phenomenon that can be blocked by ketanserin.<sup>17</sup> Animal studies have

shown that serotonin is released during platelet activation.<sup>43-45</sup> High coronary sinus blood concentrations of serotonin and increased concentrations of serotonin at sites of endothelial injury are seen in *in vivo* animal models with spontaneous occlusive coronary thrombus formation.<sup>44</sup> The cumulative evidence obtained in animal research suggested that blockade of serotonin 5-HT<sub>2</sub> receptors with ketanserin is as antithrombotic as acetylsalicylic acid in cases in which a modest insult, such as endothelial cell injury, forms the underlying cause of the thrombus; this blockade also appears to be complementary to the blockade of the platelet arachidonic acid pathway by specific inhibition of the cyclooxygenase enzyme in cases with strong platelet activation. Such a strong platelet activation may occur when deep intimal injury forms the underlying cause of the occlusion and escapes a single pharmacological intervention.<sup>12,45-47</sup> Marcos et al<sup>48</sup> found that serotonin-induced vasospasm was potentiated by indomethacin in isolated perfused bovine coronary arteries. This finding may have important clinical consequences for patients undergoing coronary angioplasty, where the endothelium is damaged, platelets accumulate, and prostanoid synthetic activity is likely compromised.<sup>48</sup> Sigal and coworkers<sup>49</sup> observed that proximal but not distal coronary spasm after balloon

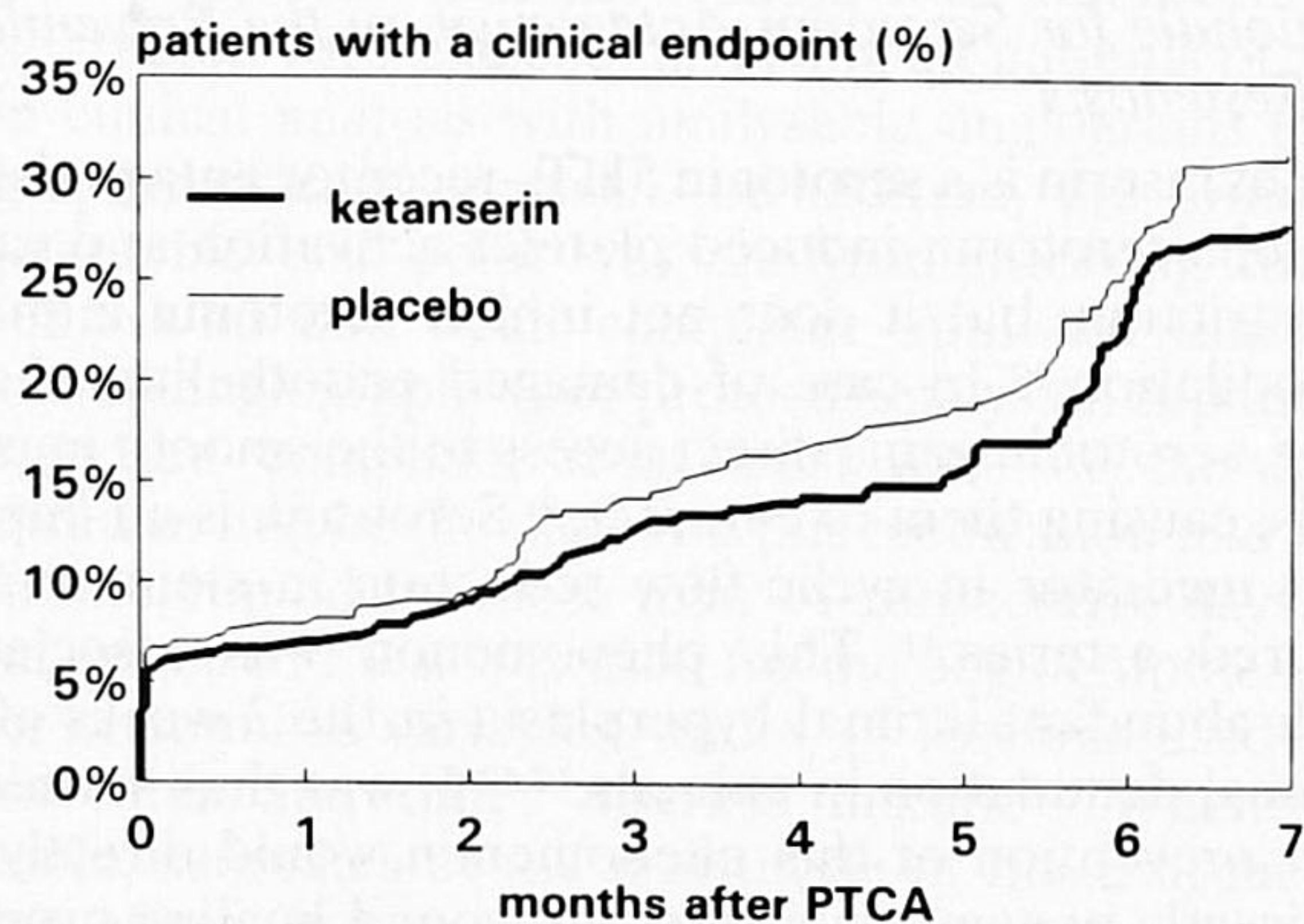


FIG 2. Cumulative distribution curve of clinical end points. PTCA indicates percutaneous transluminal coronary angioplasty.



**TABLE 5. Adverse Events In Trial Medication Groups**

	<u>Ketanserin</u>	<u>Placebo</u>	<u>All</u>	
	(n=37)	(n=39)	(n=76)	P
<b>IV loading dose</b>				
Upper abdominal complaint	3 (8)	4 (10)	7 (9)	1.00
Dizziness	5 (14)	0 (0)	5 (7)	.06
Bleeding event	6 (16)	6 (15)	12 (16)	1.00
Hypotensive event	9 (24)	4 (10)	13 (17)	.19
Dry mouth	7 (19)	2 (5)	9 (12)	.13
Arrhythmia	1 (3)	3 (8)	4 (5)	.65
Other	9 (24)	8 (21)	17 (22)	.90
None	12 (32)	20 (51)	32 (42)	.15
<b>Oral loading dose</b>	<b>(n=291)</b>	<b>(n=291)</b>	<b>(n=582)</b>	
Upper abdominal complaint	43 (15)	34 (12)	77 (13)	.33
Fatigue	49 (17)	35 (12)	84 (14)	.13
Dizziness	47 (16)	19 (7)	66 (11)	<.001
Bleeding event	22 (8)	26 (9)	48 (8)	.65
Hypotensive event	19 (7)	9 (3)	28 (5)	.08
Dry mouth	22 (8)	9 (3)	31 (5)	.03
Arrhythmia	22 (8)	10 (3)	32 (6)	.045
Other	115 (40)	102 (35)	217 (37)	.30
None	96 (33)	137 (47)	233 (40)	.001
<b>All patients</b>	<b>(n=328)</b>	<b>(n=330)</b>	<b>(n=658)</b>	
Upper abdominal complaint	46 (14)	38 (12)	84 (13)	.40
Fatigue	49 (15)	35 (11)	84 (13)	.12
Dizziness	52 (16)	19 (6)	71 (11)	<.001
Bleeding event	28 (9)	32 (10)	60 (9)	.70
Hypotensive event	28 (9)	13 (4)	41 (6)	.023
Dry mouth	29 (9)	11 (3)	40 (6)	.005
Arrhythmia	23 (7)	13 (4)	36 (5)	.12
Other	124 (38)	110 (33)	234 (36)	.26
None	108 (33)	157 (48)	265 (40)	<.001

Multiple events per patient are counted under the various headings. Numbers in parentheses are percentages. P value from continuity-adjusted  $\chi^2$  test.

dilatation can be prevented by a serotonin 5-HT<sub>2</sub> antagonist. Golino and coworkers<sup>50</sup> observed that intracoronary infusion of serotonin in patients with normal coronaries at cardiac catheterization markedly dilated the epicardial coronary arteries and increased coronary blood flow and that these effects were enhanced by the administration of ketanserin, whereas the serotonin caused profound vasoconstriction in the distal portions of coronary arteries with atherosclerosis.

Serotonin has also been shown to stimulate DNA synthesis in vascular smooth muscle cells in vitro.<sup>19,51</sup> In vitro experiments show the stimulation of mitogenesis, migration, and retraction of vascular smooth muscle cells after serotonin exposure. In low concentrations, it substantially enhances the mitogenic response of these cells to PDGF<sup>19</sup> as well as the proliferation of cultured fibroblasts and matrix synthesis.<sup>15</sup>

This mitogenic effect of serotonin can be blocked by ketanserin. When vascular smooth muscle cells are al-

lowed in vitro both to produce an extracellular matrix and intercellular junctions, addition of fresh serum stimulates the coordinate retraction of this matrix. Serotonin present in high concentrations (10<sup>-5</sup> mol/L) is important in this response, since (1) only serotonin (of all tested agents) induced a comparable degree of retraction and (2) the serum response can be blocked by 5-HT<sub>2</sub> serotonergic receptor blockers. Ketanserin also decreased the collagen content in an in vivo granuloma model, where a similar cell type has been implicated.<sup>24</sup>

In view of the earlier mentioned properties of ketanserin, its administration could have a protective effect on early and late restenosis of coronary arteries after coronary angioplasty.

#### Dosage

The selection of the intravenous starting dose of ketanserin was based on the finding that an infusion rate of 0.1 mg/min appeared to be the lowest dose that was



**TABLE 6. Quantitative Analysis: Intention-to-Treat Analysis, Lesion Values Averaged per Patient**

	Ketanserin (N=287)	Placebo (N=305)	Signifi- cance
<b>Reference diameter (mm)</b>			
Before angioplasty	2.58±0.51	2.67±0.53	
After angioplasty	2.65±0.50	2.69±0.49	NS
At follow-up	2.66±0.58	2.76±0.52	P=.02
<b>Minimal luminal diameter (mm)</b>			
Before angioplasty	0.97±0.41	0.97±0.39	
After angioplasty	1.70±0.37	1.69±0.34	NS
At follow-up	1.43±0.62	1.44±0.58	NS
<b>Difference in minimal luminal diameter (mm)</b>			
Acute gain	0.73±0.41	0.72±0.39	NS
Late loss	0.27±0.49	0.24±0.52	NS
Net gain	0.46±0.60	0.47±0.56	NS
<b>Percentage stenosis</b>			
Before angioplasty	62±15	63±14	
After angioplasty	35±11	37±9	P=.04
Follow-up	47±19	48±19	NS

Acute gain: minimal luminal diameter (MLD) after percutaneous transluminal coronary angioplasty (PTCA) minus MLD before PTCA; late loss: MLD after PTCA minus MLD at follow-up; net gain: MLD at follow-up minus MLD before PTCA.

NS indicates not significant at the  $P=.05$  level.

maximally effective in inhibiting ADP-induced or adrenaline-induced platelet aggregation *ex vivo*.<sup>52</sup> This dose was subsequently used in a pilot study in patients with coronary artery stenosis, where ketanserin administration was started after balloon angioplasty and continued for 12 hours. In the latter study, Klein and coworkers<sup>52</sup> were able to show a reduction in early (after 24 hours) but not in late (after 4 to 9 months) restenosis after balloon angioplasty.

In the design of the present trial, it was deemed advantageous to start the ketanserin infusion before the balloon inflation and its potentially disruptive effects on the arterial wall, leading to local platelet deposition and stenosis. For practical reasons, infu-

sion of trial medication could not be initiated earlier than 1 hour before the insertion of the catheter. To ensure that enough ketanserin would be "on board" during the procedure, pharmacokinetic simulations were carried out that indicated the necessity for a loading dose.

In the early phase of the trial, patients were treated according to the above dosage schedule, and some cases of periprocedural hypotension and bradycardia were observed. Due to an apparently uneven distribution of cases among the treatment groups (hypotension was reported in 7 of 37 [19%] patients in the ketanserin group and in 3 of 39 [8%] patients in the placebo group), the Ethics and Safety Committee

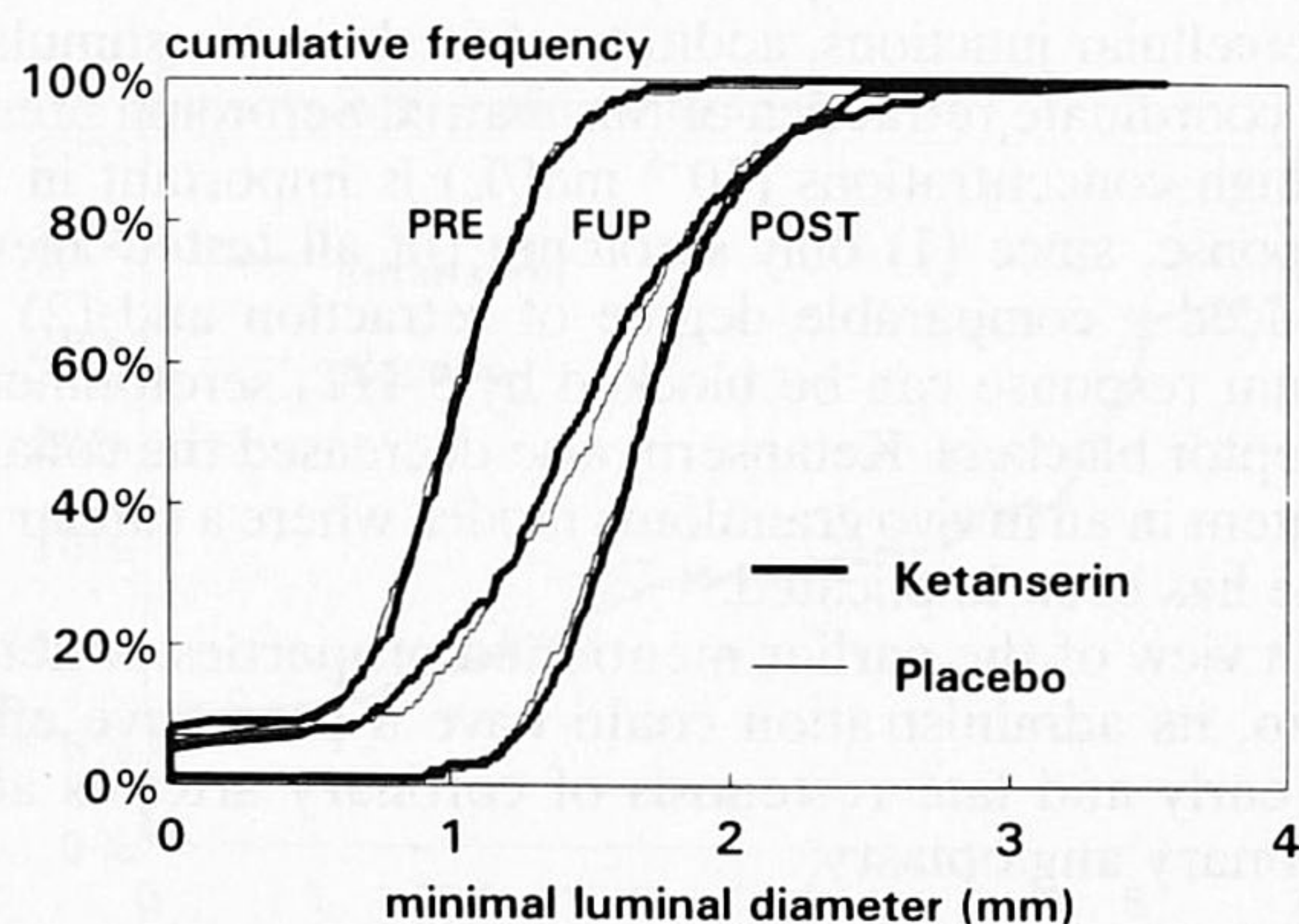


FIG 3. Cumulative distribution curve of the minimal luminal diameter before (PRE) and after (POST) percutaneous transluminal coronary angioplasty and at 6-month follow-up (FUP) in both treatment groups.

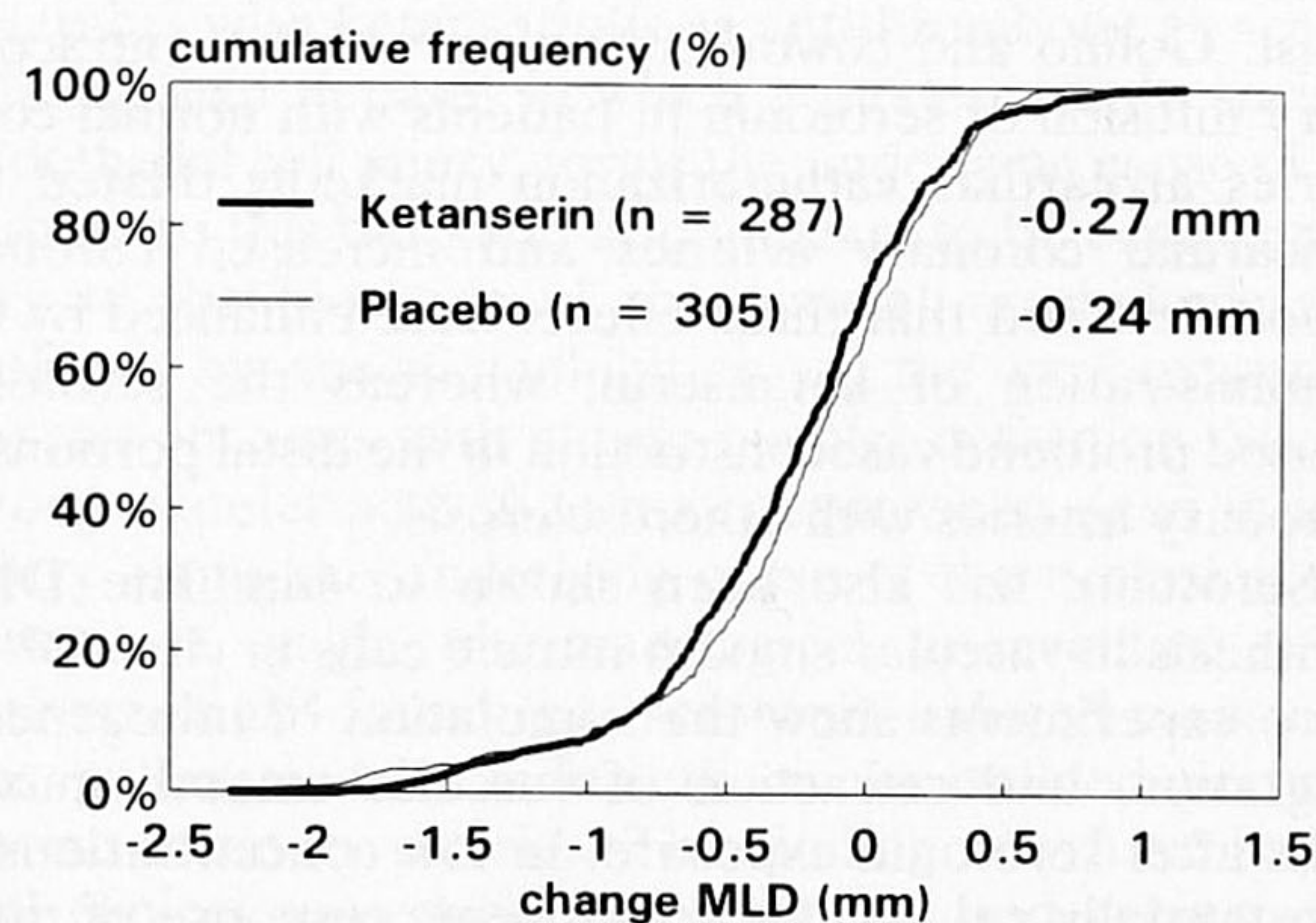


FIG 4. Cumulative distribution curve of the change in minimal lumen diameter (MLD) at follow-up respective of post-percutaneous transluminal coronary angioplasty MLD (late loss).



suggested to consider an adjustment of the dosage schedule. It was thereupon decided to leave out the intravenous administration and, instead, start with an oral tablet that was taken 1 hour before catheter insertion. This would yield plasma levels during balloon inflation that were at least similar to those obtained in the original intravenous schedule. The protocol was amended accordingly, and vasovagal reactions were found to be rare in the rest of the patients.

The oral maintenance dose was chosen such that plasma ketanserin levels would exceed  $10^{-8}$  mol/L, which is the concentration that elicits virtually complete inhibition of serotonin-induced platelet aggregation *ex vivo*. This requirement is usually met after oral ketanserin administration at the recommended antihypertensive dose (ie, 20 or 40 mg bid). Nadir plasma levels, however, may not always exceed this threshold after the lower dose, but they did after the higher (personal communication by F. De Clerck). It was, therefore, decided to select the 40 mg bid regimen as the maintenance dose in this trial.

### Trial Design

The mechanism of action of ketanserin implied that it would prevent both acute occlusion due to platelet aggregation-induced thrombus formation and late restenosis due to platelet aggregation-induced hyperplasia. As a consequence, trial medication was started before the procedure, ie, before wall injury occurred. This had major consequences for the definition of the clinical end point. On the one hand, all failures between the first balloon inflation and the end of the procedure could have been influenced by the trial medication and were therefore counted as clinical end points. On the other hand, as the aim of this trial was to study the effect of ketanserin on the inhibition of the neointimal hyperplasia after balloon wall injury, it seemed reasonable to exclude those patients from the analysis of the main clinical end point in whom no balloon inflation had occurred.

At this stage of the development of the therapeutic principle, we considered it necessary to establish the mechanism of action by direct angiographic observation of the encroachment of the lumen over a period of 6 months. For this reason, the trial was designed to have two major analytic thrusts: a comparison of clinical end points and a comparison of the loss in lumen diameter. This, however, required a compromise for the power of the trial. Based on the angiographic principle, with 300 patients per trial medication group, the trial had more than 95% power to statistically distinguish a loss in lumen diameter of 0.40 mm under placebo from 0.25 mm under ketanserin (the standard deviation of the loss in lumen diameter is known to be around 0.50 mm). Against this, the trial had only marginal power to detect differences in the rates of the primary clinical end point: with 300 patients, the power to distinguish an event rate of 25% under placebo from 15% under ketanserin was only 85%. At the end of the trial, the loss in lumen diameter under placebo turned out to be 0.24 mm. This unanticipated finding, however, eroded the power of the angiographic analysis to some extent: a similarly (40%) sized reduction from 0.25 mm to 0.15

mm could only be detected with 75% power. Over the last few years, it has become apparent that the loss in MLD in different trials could vary considerably, since in the placebo groups of the most recent trials, the loss in MLD ranged from 0.24 to 0.36 mm, although at this stage we do not have a clear explanation for this intertrial variability.<sup>53-55</sup> It is surmised that differences in baseline demographic data could have affected the mean loss in MLD at follow-up. Factors such as the percentage of recruited patients in CCS class 4, patients with recent onset of angina, unstable patients, diabetics, and the frequency of total occlusion apparently have a major impact on the loss in MLD at follow-up. In a recent editorial in *Circulation*, Popma, Califf, and Topol<sup>56</sup> recommended that in future trials high-risk patients not be excluded, so as to avoid a misrepresentation of the population of typical patients undergoing angioplasty.

One of the consequences of having systematic angiographic follow-up at 6 months is that it thwarts the natural occurrences of clinical end points (reinterventions). As a consequence, all indications for a revascularization procedure that had been triggered by the 6-month repeat angiography were counted as end points, provided that the indication was also substantiated by anginal symptoms or positive findings at exercise testing.

For the definition of the primary clinical end point, we chose a combination of the major untoward clinical events: death, myocardial infarction, referral for coronary bypass surgery, or an indication for repeat angioplasty as the major clinical end point. The advantages are obvious, as was recently indicated in the above-mentioned editorial<sup>56</sup>: the definition of the clinical end point is based on so-called hard criteria, the end point is evaluable in all randomized patients, and the end point leads to simple effect estimates with corresponding 95% confidence intervals.

The process of luminal narrowing after coronary balloon angioplasty is approximately normally distributed, with few lesions showing regression, most of the lesions showing no change, and a considerable amount of the lesions showing progression. Restenosis can thus be viewed as the tail end of a near-Gaussian distribution, with some lesions crossing a more or less arbitrary angiographic cutoff point rather than a separate disease entity that occurs in some lesions but not in others. For comparison of the angiographic efficacy of pharmacological agents, we therefore recommend the use of change of MLD as an end point rather than restenosis rate.<sup>57,58</sup> Statistically, the quantitative outcome can be evaluated with less than a third of the number of patients required for assessment of the categorical outcome. This is indeed logical because categorical end points do not take full advantage of the available information, discard quantitative information, and therefore result in loss of statistical power. For the angiographic analysis, two approaches exist: a per-lesion or a per-patient analysis. In the latter, the patient is taken as the unit of analysis by averaging lesion values per patient. Statistically, a per lesion analysis is appropriate only if the changes per lesion within patients act independently.<sup>37</sup> As we could not guarantee that this would be the case, we chose the more conservative per-patient analysis.<sup>59</sup>



### *Quantitative Angiography Versus Clinical Events as Primary End Point*

The primary goal of a restenosis prevention trial is the improvement in short- and long-term clinical outcome of patients having undergone a PTCA procedure. It is assumed that the improvement in clinical outcome is related to an anatomic phenomenon, namely the prevention of the recurrence of the stenosis in the treated vessel.<sup>54</sup> Therefore, in this type of trial, testing pharmacological compounds with possible anti-ischemic or antianginal effects unrelated to the postinjury hyperplasia, the clinical outcome might be misleading and obscure the reason for the observed improvement.

In the present study, there was a trend toward a lower incidence of revascularization procedures (repeat PTCA, CABG) in the ketanserin group (77 versus 95 in the control group). At the same time, there was also a difference in the loss in MLD from post-PTCA to follow-up, with the larger loss in MLD observed in the ketanserin group when compared with the placebo group. Although not statistically significant, these contradictory trends raise a question regarding the interpretation of the outcome of the study. If there is evidence of a lesser degree of angina, better functional performance, or as in this case, less need for repeat PTCA or CABG, this implies that the treatment may have an antianginal or anti-ischemic effect that is mediated by some other mechanism than modulation of the proliferative process in the stenotic area.

Indeed, ketanserin has a potential for accounting for such an effect. It has been demonstrated by Golino et al<sup>50</sup> that patients with angina pectoris develop marked coronary vasoconstriction in response to intracoronary injection of serotonin and that this effect was abolished after administration of ketanserin. This may have clinical significance, since coronary vasospasm and vasoconstriction play an important pathogenic role not only in variant angina but also in a wide spectrum of ischemic heart diseases such as effort angina, unstable angina, and acute myocardial infarction. There are also results suggesting that ketanserin promotes coronary blood flow by improving rheological parameters. For example, it has been shown that the deformability of erythrocytes increases<sup>60</sup> and that there is a decrease in whole blood viscosity.<sup>61</sup> Finally, a potentially antianginal mechanism may be mediated by the arteriolar dilating effect of ketanserin resulting in left ventricular unloading. These considerations are speculative, and it must be pointed out that no significant differences in blood pressure and heart rate (two major determinants of the myocardial oxygen demand) were recorded at 1-month follow-up and subsequently, although an initial significant decrease in blood pressure was observed immediately before and after the PTCA procedure in the group treated with ketanserin.

### *Possible Explanations for the Lack of Effect of Ketanserin in This Trial*

As patients were treated with ketanserin only 1 hour before PTCA, the question arises if a longer pretreatment phase might have been more effective. However, pharmacokinetic simulations with the intravenous loading dose as well as studies with oral dosing had shown enough ketan-

serin to be "on board" during the procedure to ensure adequate platelet aggregation inhibition.<sup>62-64</sup>

Similar numbers of clinical end points in each arm of the trial were encountered in the periprocedural phase. It might be inferred from these results that the preventive administration of isosorbide dinitrate at the time of the procedure had such a beneficial effect that the cardioprotecting effect of ketanserin was masked. Similarly, the administration of aspirin might have masked the potential antiserotonin effect of ketanserin in the treated group, both compounds being similarly potent in terms of platelet aggregation antagonism,<sup>65</sup> so that the additional cardioprotective effect of ketanserin could no longer be detected.

In general, the speculations mentioned before raised the question of the potential benefit of other forms of synergy. At the time of the design of the trial, it was reported that a serotonin antagonist used in synergy with a thromboxane blocker was more potent than each drug by itself.<sup>45,66,67</sup> Further investigation of serotonin antagonist in synergy with a therapeutic agent acting on associated mechanisms of restenosis might be worth pursuing. On the other hand, since there are multiple redundant metabolic pathways involved in the process of platelet aggregation and adhesion, it seems illusive and unrealistic to try to block or selectively inhibit all these multiple metabolic pathways. It has been suggested that the final pathway in the activation and exposure of the platelets could be ultimately interrupted by selectively blocking the glycoprotein receptor IIb-IIIa on the membrane of the thrombocyte.<sup>68</sup> But even then, as has been put forward, an antagonist of the glycoprotein receptor would not prevent the deposition of a single layer of platelets. Since the mitogenic factors are released from the  $\alpha$ -granules of the adherent platelets, the blockade of this final pathway would also be insufficient to prevent the initiation of the restenosis phenomenon.

As far as the antiproliferative effect of ketanserin is concerned, it has been shown that the platelet-derived 5-HT stimulates migration and proliferation of vascular smooth muscle cells<sup>19,22-25</sup> and promotes the synthesis of collagen and proteoglycans by isolated cells.<sup>24,26,27</sup> The potential role of this monoamine in neointima formation in reaction to balloon-induced damage of carotid arteries in rats with the use of pharmacological treatment with ketanserin has been studied recently.<sup>69</sup> The results suggested that serotonin in this rat model contributed to some extent to the neointima formation after vascular injury but certainly was not a dominant mediator in this respect. The absence of effect of ketanserin in the present trial may indicate that in humans this monoamine should add even less to the complex biology of late restenosis. Another possible explanation is that, although it might contribute substantially, there may be other mediators responsible, so that inhibitors of multiple mediators are required. Considering the rate of adverse events documented in the present study and the absence of clinical benefit, however, we are not recommending the isolated use of this drug for prevention of restenosis. However, further study in combination with other synergetic compounds should not be disregarded.



## Appendix

### Steering Committee

P.W. Serruys, MD (Chairman); W. Klein, MD; J. Willerson, MD; J. Pool, MD; D. Jackson, MD; R. Van Gool, MD; J. Symoens, MD.†

### Ethics and Safety Committee

A. Bruschke, MD, PhD; T.C. Chalmers, PhD; C.D. Furberg, PhD; P. Meier, PhD; J.G.P. Tijssen, PhD.

### Critical Event Committee

F. ten Cate, MD; E. Schroeder, MD; W. Wijns, MD; J. Deckers, MD; B. De Bruyne, MD.

### Park Study Group: Participating Centers and Investigators

The following institutions and investigators participated in PARK. The number of patients enrolled at each center is given in parentheses.

Freie Universität Berlin, Universitätsklinikum Rudolf Virchow/Charlottenburg, Berlin, Germany (95): W. Rutsch, MD, Principal Investigator.

Academisch Ziekenhuis Dijkzigt, Rotterdam, The Netherlands (90): P. Serruys, MD, Principal Investigator; H. Suryapranata, MD.

Onze Lieve Vrouw Ziekenhuis, Cardiovascular Center, Aalst, Belgium (89): G.R. Heyndrickx, MD, Principal Investigator; B. De Bruyne, MD; P. Nellens, MD; M. Goethals, MD; P. Goemaere, RN.

Med Clin I, Sahlgrenska Hospital, Göteborg, Sweden (70): H. Emanuelsson, MD, Principal Investigator; K. Selin, MD.

University of Leeds, England (69): S.G. Ball, MD, Principal Investigator; A.F. Mackintosh, MD; M.R. Rees, MD.

Medizinische Universitätsklinik, Graz, Austria (65): W. Klein, MD, Principal Investigator; B. Eber, MD; O. Luha, MD.

Clinique Universitaire St Luc, University of Louvain Medical Schools, Brussels, Belgium (46): W. Wijns, MD, Principal Investigator; J. Cosyns, MD; O. Decoster, MD; M. Delgadillo; C. Hanet, MD.

Clinique de Mont-Godinne, University of Louvain Medical School, Yvoir, Belgium (40): E. Schroeder, MD, Principal Investigator; R. Kremer, MD; B. Marchandise, MD; P. Chenu, MD.

Emory University, Atlanta, Ga (34): H.A. Liberman, MD, Principal Investigator.

University of Texas Medical School, Houston (28): J.T. Willerson, MD, Principal Investigator; A.V. Adyanthaya, MD; D.B. Cassidy, MD; K.L. Gould, MD; R. Smalling, MD; H.V. Anderson, MD.

Veterans Administration Medical Center, Dallas, Tex (28): E. Eichhorn, MD, Principal Investigator.

Henry Ford Hospital, Detroit, Mich (25): F. Khaja, MD, Principal Investigator; J. Brymer, MD; S. Goldstein, MD; P. Kraft, MD; T. McFarland, MD.

Emory University, Atlanta, Ga (14): R.W. Alexander, MD, Principal Investigator; S.B. King, MD; H.A. Liberman, MD; D.C. Morris, MD.

Beth Israel Hospital, Boston, Mass (11): D. Baim, MD, Principal Investigator; M.J. Levine, MD; G. Reis, MD.

### Data Coordinating and Analysis Center

Cardialysis BV, Rotterdam, The Netherlands: R. Melkert, MD; J. Tijssen, PhD; J. Pool, MD.

### Quantitative Angiographic Core Laboratory

Cardialysis BV/Thorax Center, Rotterdam, The Netherlands: P.W. Serruys, MD; B.J. Rensing, MD; W.R.M. Hermans, MD; J.P.R. Herrman, MD; J. Pameijer.

### Janssen Research Foundation

J. Symoens, MD; R. Van Gool, MD; G. Sieben; A.G. Dupont, MD. Trial Monitors: B. Bohanek (USA); R. Van Gool, MD; H.W. Scheijgrond; S. Versele (Belgium), H.P. Benn, MD (Germany); J.C. van Oene, PhD (The Netherlands); B. Lundgren, PhD (Sweden); M.B. O'Donovan (United Kingdom); W. Pfeffer, MD (Austria).

### Study Directors

J. Pool, MD, for Cardialysis and J. Symoens, MD,† and R. Van Gool, MD, for the Janssen Research Foundation.

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†Dr Symoens died during the course of the trial.



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