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A COMPARISON OF BALLOON-EXPANDABLE–STENT IMPLANTATION WITH BALLOON ANGIOPLASTY IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract *Background.* Balloon-expandable coronary-artery stents were developed to prevent coronary restenosis after coronary angioplasty. These devices hold coronary vessels open at sites that have been dilated. However, it is unknown whether stenting improves long-term angiographic and clinical outcomes as compared with standard balloon angioplasty.

Methods. A total of 520 patients with stable angina and a single coronary-artery lesion were randomly assigned to either stent implantation (262 patients) or standard balloon angioplasty (258 patients). The primary clinical end points were death, the occurrence of a cerebrovascular accident, myocardial infarction, the need for coronary-artery bypass surgery, or a second percutaneous intervention involving the previously treated lesion, either at the time of the initial procedure or during the subsequent seven months. The primary angiographic end point was the minimal luminal diameter at follow-up, as determined by quantitative coronary angiography.

Results. After exclusions, 52 patients in the stent group (20 percent) and 76 patients in the angioplasty group (30 percent) reached a primary clinical end point (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; P = 0.02). The difference in clinical-event rates was explained mainly by a reduced need for a second coronary angioplasty in the stent group (relative risk, 0.58; 95 percent confidence interval, 0.40 to 0.85; P = 0.005). The mean (±SD) minimal luminal diameters immediately after the procedure were 2.48±0.39 mm in the stent group and 2.05±0.33 mm in the angioplasty group; at follow-up, the diameters were 1.82±0.64 mm in the stent group and 1.73±0.55 mm in the angioplasty group (P = 0.09), which correspond to rates of restenosis (diameter of stenosis, ⩾50 percent) of 22 and 32 percent, respectively (P = 0.02). Peripheral vascular complications necessitating surgery, blood transfusion, or both were more frequent after stenting than after balloon angioplasty (13.5 vs. 3.1 percent, P<0.001). The mean hospital stay was significantly longer in the stent group than in the angioplasty group (8.5 vs. 3.1 days, P<0.001).

Conclusions. Over seven months of follow-up, the clinical and angiographic outcomes were better in patients who received a stent than in those who received standard coronary angioplasty. However, this benefit was achieved at the cost of a significantly higher risk of vascular complications at the access site and a longer hospital stay. (N Engl J Med 1994;331:489-95.)

IMPLANTATION of an intracoronary stent in conjunction with balloon angioplasty is not only highly effective in treating acute vessel closure due to balloon-induced dissection, but it may also reduce the rate of restenosis.[1-4] Unfortunately, all stents currently available are metallic and thus thrombogenic, a problem that necessitates anticoagulation therapy.[5,6] This therapy exposes the patient to an increased risk of major bleeding and vascular complications, which may prolong the hospital stay.[7] Despite these drawbacks and although the superiority of stent implantation over standard balloon angioplasty has not yet been proved, stenting has been used increasingly. Therefore, we conducted a multicenter, randomized study comparing stent implantation and balloon angioplasty with respect to their safety and efficacy

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in patients with stable angina pectoris and a single new lesion in a coronary artery.

Methods

Selection of Patients

Patients scheduled to undergo coronary angioplasty because of stable angina due to a single new lesion in a coronary artery were eligible for the study if they had no contraindication to anticoagulant or antiplatelet therapy and if they were also suitable candidates for coronary bypass surgery. The target lesion needed to be less than 15 mm long and to be located in a vessel more than 3 mm in diameter that supplied normally functioning myocardium. Patients with an ostial lesion, a lesion at a bifurcation, or a lesion in a previously grafted vessel were excluded from the study, as were patients in whom an intracoronary thrombus was suspected.

The study was carried out according to the principles of the Declaration of Helsinki. Oral or written informed consent according to local practice was obtained for every patient.

Randomization

Patients were randomly assigned by telephone from a central office to either implantation of a Palmaz–Schatz stent or balloon angioplasty. To ensure an equal distribution of treatments in each center, we developed the randomization sequence on a site basis in blocks of six treatment assignments.

Balloon Angioplasty and Stent Implantation

Balloon angioplasty and stent implantation were performed according to standard clinical practice by the femoral approach. The stent was deployed by inflating a balloon over which the collapsed stent was fitted. Inflation of the balloon expanded the stent. After the implantation of the stent, the stented area was often dilated further by standard balloon angioplasty. All patients received 250 to 500 mg of aspirin daily and 75 mg of dipyridamole three times a day; this treatment was started the day before the procedure and was continued for six months. During the procedure, patients receiving a stent were treated with a continuous infusion of dextran (1000 ml) and a bolus dose of 10,000 U of heparin, repeated if necessary, followed by a combination of heparin and oral anticoagulation therapy (with warfarin) after the removal of the sheath and titrated by measuring the prothrombin time and either the activated partial-thromboplastin time or the activated clotting time. The dose of heparin was decreased progressively after the prothrombin time had been in the therapeutic range (international normalized ratio, 2.5 to 3.5) for at least 36 hours. Warfarin therapy was continued for three months. The patients who underwent balloon angioplasty received only 10,000 U of heparin during that procedure, followed by an additional bolus dose or a continuous infusion if deemed necessary. In addition, both treatment groups received calcium antagonists until discharge from the hospital.

Clinical and Angiographic Follow-up

Patients were seen in the outpatient clinic after one, three, and six months for an interview, physical examination, and electrocardiogram. Exercise testing was performed before the second cardiac catheterization and coronary angiography at six months. If a revascularization procedure involving the treated segment had been performed before the six-month angiography, the most recent angiogram obtained before this intervention, if available, was used as the follow-up angiogram, regardless of the timing of the second intervention. If the time to follow-up angiography was less than three months and no second intervention was performed, the patient was asked to undergo angiography again at six months. In the absence of a second angiogram at six months, the angiogram obtained most recently within the previous three months was used, if available, provided that no end point had occurred.

Three angiograms were obtained for each patient — one just before the intervention, one immediately after, and one at follow-up. All the angiograms were analyzed by the Cardiovascular Angiography Analysis System and sent to the core laboratory (Cardialysis, Rotterdam, the Netherlands). To standardize the method of data acquisition and to ensure the exact reproducibility of the angiograms performed after the intervention and at follow-up, measurements were made as described earlier.[8]

End Points

The primary clinical end points were whichever of the following occurred first: death, a cerebrovascular accident, myocardial infarction, bypass surgery, or a second percutaneous intervention involving the previously treated lesion between the time of the initial procedure and the angiography performed at 6 months (±4 weeks) (or at 7 months if no angiography was performed at 6 months). The indication for a second intervention or for bypass surgery had to be substantiated by symptoms or by electrocardiographic or scintigraphic evidence of myocardial ischemia at rest or during exercise. All events were reviewed by the critical-event committee, which was unaware of the treatment assignments.

Death was defined to include all deaths, regardless of cause. Cerebrovascular accidents occurring in patients receiving anticoagulant therapy were considered to be intracranial hemorrhages unless unequivocally demonstrated otherwise. Myocardial infarction was diagnosed if there were new pathologic Q waves according to the Minnesota Code[9] or if there was an increase in serum creatine kinase to more than twice the normal value, together with a pathologic increase in myocardial isoenzymes. Bypass surgery was defined to include emergency or elective bypass surgery involving the previously treated segment. Emergency bypass surgery was defined as involving an immediate transfer from the angioplasty suite to the operating room during the initial phase of treatment. "Bailout" stent implantation was defined as the placement of a stent in the event of Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow after angioplasty or in the case of worsening of the base-line TIMI flow by one grade.[10] In all instances, prolonged balloon angioplasty had to be attempted before bailout stenting was considered. By design, stent implantation as a bailout procedure was considered equivalent to emergency bypass surgery but was removed retroactively from the analysis of primary end points, since it is currently perceived as an integral part of an angioplasty strategy. Only the untoward clinical events associated with such stenting were counted as end points. Second interventions were those involving a previously treated lesion that followed the initial procedure, which was considered complete when the guiding catheter was removed from the arterial sheath. Revascularization (surgical or percutaneous) involving other coronary arteries did not constitute an end point.

The primary angiographic end point was the minimal luminal diameter at follow-up. For each treated segment, this value was calculated from the mean values obtained in multiple matched projections.

Secondary end points included (1) the angiographic success rate, defined as the rate of achievement of less than 50 percent stenosis on visual assessment; (2) the procedural success rate, defined as the rate of achievement of less than 50 percent stenosis on quantitative assessment, without the occurrence of clinical events during the hospital stay; (3) the functional class according to the classification of the Canadian Cardiovascular Society at six months or at the time of intercurrent angiography and second intervention; (4) the results of exercise testing at six months or earlier, if clinically indicated; (5) the rate of restenosis (stenosis $\geq$50 percent at follow-up) at six months.

Power Calculations and Statistical Analysis

At the outset of the study, the size of the required sample (428 patients) was based on an assumed rate of clinical events of 30 percent in the angioplasty group and a reduction of that rate by 40 percent in the stent group (by a two-sided test with an alpha error of 0.05 and a power of 0.80). To compensate for unsuccessful interventions and losses to follow-up, the sample was enlarged by 10 percent (to 470 patients). In addition, to adjust for a loss of power due to a planned interim analysis, the sample was increased by another 10 percent, reaching a final size of 520 patients.[11]

The main clinical analysis consisted of a single comparison be-

tween the two study groups with respect to the primary clinical end point, regardless of its time of occurrence; this analysis involved all randomized patients with the exceptions of three patients found after randomization not to be eligible and of one patient who withdrew informed consent for further treatment and follow-up according to the intention-to-treat principle. The clinical events were ranked according to the highest category of severity on the following scale: death, cerebrovascular accident, myocardial infarction, emergency bypass surgery, elective bypass surgery, and repeat percutaneous intervention.

The main angiographic analysis consisted of a single comparison between the two study groups with respect to minimal luminal diameter and was performed according to the intention-to-treat principle.

Continuous variables are expressed as means ±SD and were compared by the unpaired Student's t-test. The chi-square test with Yates' correction was used to compare proportions. Discrete variables are expressed as counts and percentages and are compared in terms of relative risks (for stenting as compared with angioplasty), with 95 percent confidence intervals calculated by the formula of Greenland and Robins.[12] All statistical tests were two-tailed.

Results

Characteristics of the Patients

Between June 1991 and March 1993, 520 patients were randomly assigned to stent implantation (262 patients) or balloon angioplasty (258 patients) at 28 participating centers. Of these 520 patients, 4 were excluded from further analysis, 3 in the stent group and 1 in the angioplasty group. One patient withdrew his informed consent and left the hospital without receiving treatment, two other patients did not undergo coronary revascularization because their lesions proved to be unimportant during on-line quantitative coronary angiography at the time of the intended intervention, and one patient participated in another study with an investigational drug. There were no differences in base-line characteristics between the two study groups (Tables 1 and 2).

In-Hospital Clinical Outcomes

Of the remaining 259 patients randomly assigned to receive stents, 14 (5.4 percent) did not receive a stent but were treated successfully with balloon angioplasty. The reasons for this crossover were the withdrawal of informed consent in five, the physician's preference because of the patient's unfavorable anatomy (e.g., small vessel size) or angiographic evidence of thrombus in three, and failure to cross the lesion with the stent in six. In addition, stent implantation was unsuccessful in 10 patients: 6 because the lesion was not dilated beforehand and 4 because the stent could not be deployed. Of these 10 patients, 8 underwent bypass surgery that was urgent in 3 and elective in 5. The remaining two patients, who unexpectedly had totally occluded coronary arteries that could not be recanalized, were treated medically.

Of the 257 remaining patients randomly assigned to balloon angioplasty, 13 (5.1 percent) received stents for the following reasons: acute vessel closure in 1, flow-limiting dissection in 11, and a suboptimal angiographic result in 1. Of these 13 patients, 2 were referred for urgent bypass surgery and 1 had a non–Q-wave myocardial infarction. In addition, three other patients who had complicated balloon angioplasty and in whom no bailout stent implantation was attempted underwent urgent bypass surgery. Therefore, the angiographic success rate was 96.9 percent in the stent group and 98.1 percent in the angioplasty group, whereas the procedural success rates were 92.7 and 91.1 percent, respectively.

Table 1. Base-Line Clinical Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis.*

Characteristic	Angioplasty (N = 257)	Stent (N = 259)
Age (yr)	58±10	57±9
Weight (kg)	79±13	78±11
Height (cm)	171±9	171±8
	no. (%)	*no. (%)*
Male sex	212 (82)	207 (80)
Ever smoked	124 (48)	119 (46)
Current smoker	60 (23)	62 (24)
Diabetes mellitus	16 (6)	17 (7)
Previous conditions		
Myocardial infarction	48 (19)	52 (20)
Coronary-artery bypass grafting	5 (2)	0
Angioplasty	8 (3)	5 (2)
Hypertension	89 (35)	80 (31)
Hypercholesterolemia	95 (37)	89 (34)
Stroke	6 (2)	6 (2)
Peripheral vascular disease	8 (3)	10 (4)
Exertional angina (CCS class)†		
I	9 (4)	9 (3)
II	75 (29)	82 (32)
III	130 (51)	125 (48)
IV	20 (8)	16 (6)
None	23 (9)	27 (10)
Mixed	89 (35)	89 (34)

*Plus–minus values are means ±SD.

†According to the classification system of the Canadian Cardiovascular Society (CCS).

The ranking and the total number of clinical events occurring in the hospital are shown in Table 3. The composite rate for all in-hospital events was similar in both groups (16 events or 6.2 percent in the angioplasty group vs. 18 events or 6.9 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.58 to 2.14). There were no in-hospital deaths in either group; one patient treated with balloon angioplasty had an intracranial hemorrhage. There was no difference between groups in the incidence of Q-wave and non–Q-wave infarction (3.1 percent in the angioplasty group vs. 3.4 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.44 to 2.85) or in the need for urgent or elective cardiac surgery or second angioplasty during the hospital stay (2.7 percent in the angioplasty group vs. 3.5 percent in the stent group; relative risk, 1.28; 95 percent confidence interval, 0.48 to 3.37).

Angiographically documented stent thrombosis during the hospital stay occurred in 3.5 percent of patients, an incidence similar to that of subacute vessel closure after balloon angioplasty (2.7 percent). It is noteworthy that no stent thrombosis occurred in the 13 patients treated with a bailout stent. However, the incidence of bleeding and vascular complications was

significantly higher after stent implantation than after balloon angioplasty (13.5 vs. 3.1 percent; relative risk, 4.34; 95 percent confidence interval, 2.05 to 9.18; $P<0.001$).

The mean hospital stay was 8.5 days in the stent group and 3.1 days in the angioplasty group ($P<0.001$).

Clinical Outcomes at Seven Months

The numbers of various types of clinical events at seven months among all 516 patients are shown in Table 3. A primary clinical end point was reached by 76 of the 257 patients randomly assigned to balloon angioplasty (30 percent), as compared with 52 of the 259 patients randomly assigned to stent implantation (20 percent) (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; $P = 0.02$). This difference in long-term clinical outcome is shown in the cumulative distribution curves for the primary clinical end point in both treatment groups (Fig. 1D). The favorable long-term outcome in the stent group was also partly reflected in the difference between the two groups in functional class at the time of the second angiography (Table 4). The most striking difference in clinical outcomes was the significantly reduced need for an elective second revascularization by means of percutaneous intervention involving the target lesion. There was a 42 percent reduction favoring stent implantation.

During the study, three patients died, one in the

Table 2. Angiographic Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis and Characteristics of the Procedures They Underwent.*

Characteristic	Angioplasty (N = 257)	Stent (N = 259)
	number (percent)	
Artery dilated		
Right coronary	72 (28)	60 (23)
Left anterior descending	159 (62)	165 (64)
Left circumflex	26 (10)	34 (13)
Type of lesion†		
Concentric	118 (46)	130 (50)
Eccentric		
IA	33 (13)	34 (13)
IB	62 (24)	57 (22)
IIA	10 (4)	10 (4)
IIB	13 (5)	10 (4)
Tandem	0	1 (0.4)
Multiple irregularities	21 (8)	16 (6)
Occluded (TIMI 0 or 1)‡	5 (2)	9 (3)
Calcified	27 (11)	29 (11)
Length (mm)	6.96±2.57	7.06±2.56
Thrombus after procedure§	10 (4)	3 (1)
Dissection¶		
No	145 (56)	215 (83)
Type A	43 (17)	21 (8)
Type B	57 (22)	16 (6)
Type C	9 (4)	5 (2)
Type E	1 (0.4)	1 (0.4)
Type F	2 (0.8)	0
Nominal size, stent or balloon (mm)	3.29±0.38	3.31±0.34
Balloon/stent artery ratio	1.12±0.15	1.12±0.15
Largest balloon size (mm)‖	3.30±0.38	3.40±0.40
Maximal pressure (atmospheres)	9±3	10±8
Total inflation time (sec)	399±359	180±178

*The interobserver and intraobserver variability of these morphologic measures has previously been reported by the core laboratory.[13] Plus–minus values are means ±SD.

†According to the classification system of Ambrose et al.[14]

‡According to the TIMI Study Group.[10]

§According to the definition of Ellis et al.[15]

¶According to the classification system of Dorros et al.[16]

‖Nominal size.

Table 3. Frequency of Primary Clinical End Points in the Hospital and at Seven Months in Descending Order of Severity, Total Number of Events, and Quantitative Comparison of Immediate and Long-Term Angiographic Results.*

Event	Angioplasty (N = 257)	Stent (N = 259)	Relative Risk (95% CI)
	number (percent)		
Death			
In hospital	0	0	—
At 7 mo	1 (0.4)	2 (0.8)	1.98 (0.18–21.75)
All events	1 (0.4)	2 (0.8)	1.98 (0.18–21.75)
Cerebrovascular accident			
In hospital	1 (0.4)	0	—
At 7 mo	2 (0.8)	0	—
All events	2 (0.8)	0	—
Q-wave MI			
In hospital	2 (0.8)	5 (1.9)	2.48 (0.49–12.67)
At 7 mo	4 (1.6)	7 (2.7)	1.74 (0.51–5.86)
All events	5 (1.9)	7 (2.7)	1.39 (0.45–4.32)
Non–Q-wave MI			
In hospital	6 (2.3)	4 (1.5)	0.66 (0.19–2.32)
At 7 mo	6 (2.3)	4 (1.5)	0.66 (0.19–2.32)
All events	7 (2.7)	4 (1.5)	0.57 (0.17–1.91)
Urgent CABG			
In hospital	4 (1.6)	5 (1.9)	1.24 (0.34–4.57)
At 7 mo	4 (1.6)	5 (1.9)	1.24 (0.34–4.57)
All events	5 (1.9)	6 (2.3)	1.19 (0.37–3.85)
Elective CABG			
In hospital	0	3 (1.2)	—
At 7 mo	6 (2.3)	8 (3.1)	1.32 (0.47–3.76)
All events	6 (2.3)	10 (3.9)	1.65 (0.61–4.48)
Repeat PTCA			
In hospital	3 (1.2)	1 (0.4)	0.33 (0.03–3.16)
At 7 mo	53 (20.6)	26 (10.0)	0.49 (0.32–0.75)
All events	60 (23.3)	35 (13.5)	0.58 (0.40–0.85)
Any event			
In hospital	16 (6.2)	18 (6.9)	1.12 (0.58–2.14)
At 7 mo	76 (29.6)	52 (20.1)	0.68 (0.50–0.92)

Variable†	Angioplasty (N = 240)	Stent (N = 237)	P Value
	mean ±SD		
Reference diameter (mm)			
Before	3.01±0.46	2.99±0.45	NS
After	3.09±0.44	3.16±0.43	0.045
Follow-up	3.05±0.49	2.96±0.48	0.04
Minimal luminal diameter (mm)			
Before	1.08±0.31	1.07±0.33	NS
After	2.05±0.33	2.48±0.39	<0.001
Follow-up	1.73±0.55	1.82±0.64	0.09‡
Stenosis (%)			
Before	64±10	64±10	NS
After	33±8	22±8	<0.001
Follow-up	43±16	38±18	0.003
Restenosis rate (%)	32	22	0.02
Gain (mm)	0.97±0.39	1.40±0.44	<0.001
Loss (mm)	0.32±0.47	0.65±0.57	<0.001
Net gain (mm)	0.65±0.59	0.75±0.66	0.09

*"All events" refers to the total count of events at seven months (i.e., if a patient required repeat angioplasty and later coronary-artery bypass grafting, the total count at seven months would reflect both events, not just the first that occurred). CI denotes confidence interval, MI myocardial infarction, CABG coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and NS not significant.

†Reference values are the interpolated diameters of normal vessels; gain, the minimal luminal diameter after the procedure minus the value obtained before the procedure; loss, the minimal luminal diameter after the procedure minus the follow-up value; and net gain, the minimal luminal diameter at follow-up minus the value obtained before the procedure.

‡$P = 0.08$ and $P = 0.03$ for the difference in minimal luminal diameter between the two study groups at follow-up when the pre-intervention lumen and vessel size, respectively, were used as covariates.

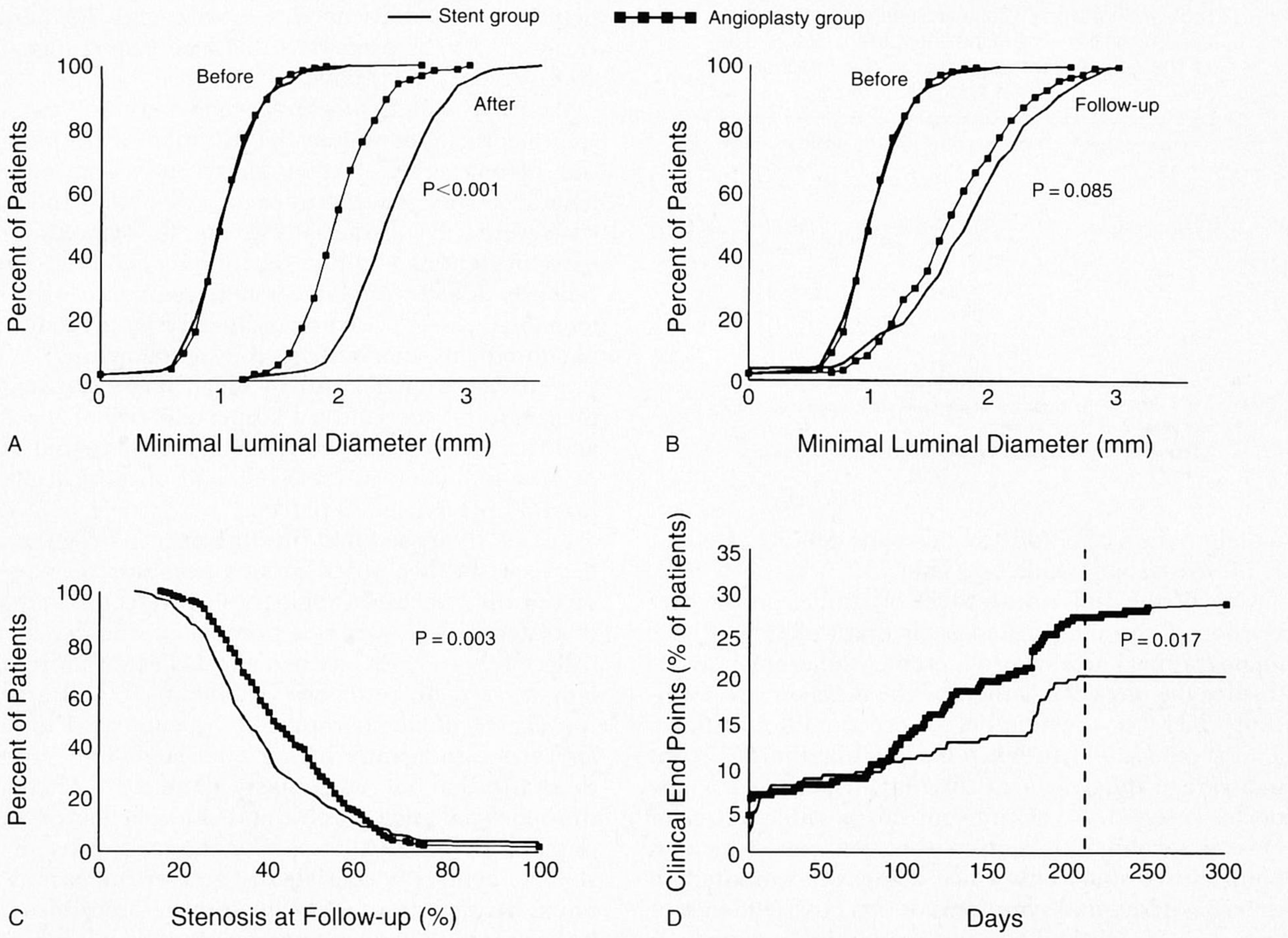

Figure 1. Cumulative Frequency Distribution Curves for the Two Study Groups, Showing Minimal Luminal Diameters Measured before and after Intervention and at Follow-up, the Percentage of Stenosis at Follow-up, and the Percentage of Patients with Clinical End Points.

Significant differences were apparent that consistently favored the stent group over the angioplasty group with respect to the increased minimal luminal diameter at intervention (Panel A) and follow-up (Panel B), the percentage of stenosis at follow-up (Panel C), and the incidence of major clinical events (Panel D). The vertical dashed line in Panel D indicates the end of the study.

angioplasty group and two in the stent group. One patient treated with balloon angioplasty committed suicide four months after the intervention. Two other patients died two and three weeks after successful stent implantations. In the first of these patients, death was preceded by chest pain associated with ST-segment elevation and was therefore thought to be related to a subacute occlusion. In the second patient, the cause of death was hypovolemic shock during surgical repair of an arteriovenous fistula. Although the stent was patent at the time of the pathological examination, the death was considered to be related to the stent.

Angiographic Analysis

Angiographic follow-up data were obtained for 93 percent of the eligible patients (Table 3). The minimal luminal diameter at follow-up was greater after stent implantation than after balloon angioplasty (1.82±0.64 vs. 1.73±0.55 mm, P = 0.09; median difference, 0.17 mm). The cumulative distribution of the minimal luminal diameter and percentage of stenosis are shown in Figure 1A, B, and C. The incidence of restenosis (the criterion for which was ≥50 percent stenosis) was 22 percent after stent implantation as compared with 32 percent after balloon angioplasty (P = 0.02).

Discussion

We found that implantation of coronary stents in patients with stable angina and a single new coronary-artery lesion was associated with a rate of immediate clinical success similar to that of standard balloon angioplasty, but a significantly lower rate of restenosis. This translated into a superior long-term clinical outcome, mainly due to a reduced need for additional percutaneous intervention, at least according to the composite analysis of clinical end points. The advantage of this combined clinical end point is that it leads to a simple estimate of the effect of treatment. However, this analysis ignores the relative effect of various events (i.e., it considers death, a cerebrovascular accident, myocardial infarction, and the like to be equally harmful to the patient) and does not reflect the multiplicity of events that may occur (e.g., in a patient undergoing second angioplasty and surgery and ulti-

Table 4. Functional Class at Seven Months of Follow-up or at the Time of the Intercurrent Intervention for the 516 Patients Included in the Intention-to-Treat Analysis.*

FUNCTIONAL CLASS†	ANGIOPLASTY (N = 257)	STENT (N = 259)
	number (percent)	
0 (Asymptomatic)	170 (66)	190 (73)
1–4	83 (32)	67 (26)
1	10 (4)	12 (5)
2	32 (12)	28 (11)
3	28 (11)	15 (6)
4	13 (5)	12 (5)
Unknown	4 (2)	2 (0.8)

*P = 0.07 for the comparison of functional classes according to treatment group (angioplasty vs. stent).

†The classes shown are those established by the Canadian Cardiovascular Society.

mately dying). To address this shortcoming, a count of all events is included in Table 3.

One of the major drawbacks of studies on the prevention of coronary restenosis is that at follow-up the angiographic knowledge of coronary anatomy may influence the physician's therapeutic decision and artificially increase the number of second interventions. This is especially true when the investigator is not kept unaware of the treatment assignments, as when a new device is tested. To circumvent this possible source of bias, a second intervention was considered an end point in this study only when it was substantiated on the basis of anginal symptoms or objective evidence of ischemia (Table 5). Only two second interventions in the angioplasty group and one in the stent group might not have been justified. Moreover, the fact that the cumulative curves for the composite clinical end points (Fig. 1D) diverged between day 75 and day 150 indicates that the difference in clinical outcome was not artificially driven by the angiographic findings at the time of the second catheterization.

Not unexpectedly, the incidence of major bleeding complications was significantly higher in the stent group (13.5 percent) than in the angioplasty group (3.1 percent). The overall incidence reported in the literature, expressed as a weighted average of groin hematomas and pseudoaneurysms, was 7.5 percent (range, 2.7 to 26 percent) and 4.2 percent (range, 0 to 10.8 percent), respectively.[17]

Another significant difference between the two treatment groups was in the duration of hospitalization. However, Cohen et al. recently showed that length of stay, consumption of resources, and total costs were still substantially greater for bypass surgery than for stenting and that the initially higher in-hospital costs of stent implantation as compared with balloon angioplasty are compensated for by the reduction in subsequent interventions during follow-up.[18,19] The practitioner and the patient must, however, weigh a long hospital stay and a 13.5 percent risk of bleeding and vascular complications against the potential benefit of a reduction in the likelihood of clinical events from 30 percent to 20 percent.

It may be argued that the difference in drug therapy between the two study groups accounts for the observed differences in angiographic outcome and rate of restenosis. However, a number of clinical studies collectively rule out any beneficial effect of anticoagulant therapy on restenosis in humans.[20-25] Moreover, the degree of angiographically documented luminal loss was significantly higher after stent implantation than after balloon angioplasty (Table 3). Therefore, the beneficial angiographic and clinical effects of stent implantation are explained by the propensity of the stent to achieve a consistently greater increase in luminal diameter immediately after the procedure than is the case with balloon angioplasty, which is inherently limited by the well-described phenomenon of elastic recoil.[3,26]

It should be emphasized that in interpreting the favorable results observed in this trial, the restrictive nature of the criteria for inclusion and exclusion must be kept in mind, and thus the results may not be generalizable to other patients, indications, and types of stents. Finally, bleeding and vascular complications and the prolonged hospitalization remain major drawbacks of stent implantation and continue to hamper its acceptance in clinical practice.

Table 5. Presence of Clinical Symptoms, Ischemic Signs, and Degree of Stenosis in Patients Who Underwent a Second Intervention at Follow-up.

VARIABLE*	ANGIOPLASTY (N = 257)	STENT (N = 259)
No. of patients	59	34†
No. with angina	54	31
No. with ECG changes at rest or during exercise	14	8
No. with neither angina nor ECG changes	2	1
No. with ETT performed	24	14
Percent stenosis — mean ±SD	59±14	66±21‡

*ECG denotes electrocardiographic, and ETT exercise-tolerance test.

†The relative risk as compared with the angioplasty group was 0.57 (95 percent confidence interval, 0.39 to 0.84; P = 0.005).

‡P = 0.06 for the comparison of groups by unpaired Student's t-test.

APPENDIX

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

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Steering Committee: P.W. Serruys (chairman), H. Emanuelsson, G.R. Heyndrickx, P.P.T. de Jaegere, F. Kiemeneij (co-chairman), C. Macaya, J. Marco, and P. Materne.

Critical Event Committee: F. Kiemeneij (chairman), P.W. Serruys, P.P.T. de Jaegere, P.J. de Feyter, and P. van den Heuvel.

Angiographic Assessment Committee: P.P.T. de Jaegere (chairman), P.W. Serruys, W. Rutsch, B. de Bruyne, and V. Legrand.

Exercise Testing Committee: V. Legrand (chairman), G. Laarman, and N. Danchin.

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