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Continued Benefit of Coronary Stenting Versus Balloon Angioplasty: One-Year Clinical Follow-Up of Benestent Trial

CARLOS MACAYA, MD, PATRICK W. SERRUYS, MD, FACC, PETER RUYGROK, MD, HARRY SURYAPRANATA, MD, GIJS MAST, MD, SILVIO KLUGMANN, MD, PHILIPPE URBAN, MD, PETER DEN HEIJER, MD, KAREL KOCH, MD, RUDIGER SIMON, MD, MARIE-CLAUDE MORICE, MD, PETER CREAN, MD, HANS BONNIER, MD, WILLIAM WIJNS, MD, NICOLAS DANCHIN, MD, CLAUDE BOURDONNEC, MD, MARIE-ANGÈLE MOREL, MSc, FOR THE BENESTENT STUDY GROUP

Objectives. **This study sought to determine the 1-year clinical follow-up of patients included in the Benestent trial.**

Background. **The Benestent trial is a randomized study comparing elective Palmaz-Schatz stent implantation with balloon angioplasty in patients with stable angina and a de novo coronary artery lesion. Seven-month follow-up data have shown a decreased rate of restenosis and fewer clinical events in the stent group. It is not established whether this favorable clinical outcome is maintained for longer periods or whether coronary stenting defers restenosis and its subsequent clinical manifestations.**

Methods. **To clarify this uncertainty, we updated clinical information on all but 1 of 516 patients enrolled in the Benestent trial (257 in balloon group, 259 in stent group) at least 12 months after the intervention. Major clinical events (primary clinical end point) were tabulated according to the intention to treat principle and included death, the occurrence of a cerebrovascular accident, myocardial infarction, the need for bypass surgery or a further percutaneous intervention in the previously treated lesion.**

Results. **After 1 year, no significant differences in mortality (1.2% vs. 0.8%), stroke (0.0% vs. 0.8%), myocardial infarction (5.0% vs. 4.2%) or coronary bypass graft surgery (6.9% vs. 5.1%) were found between the stent and balloon angioplasty groups, respectively. However, the requirement for a repeat angioplasty procedure was significantly lower in the stent group (10%) than the balloon angioplasty group (21%, relative risk [RR] 0.49, 95% confidence interval [CI] 0.31 to 0.75, p = 0.001), and overall primary end points were less frequently reached by stent group patients (23.2%) than those in the balloon group (31.5%, RR 0.74, 95% CI 0.55 to 0.98, p = 0.04). No differences were found between groups with respect to functional class angina and prescribed medication at the time of follow-up.**

Conclusions. **These clinical follow-up data show that the benefit of elective native coronary artery stenting in patients with stable angina is maintained to at least 1 year after the procedure and results in a significantly reduced requirement for repeat intervention.**

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Despite considerable technical improvement in coronary balloon angioplasty, the restenosis process remains the major limitation of this interventional technique (1–3). Restenosis has been found to be unresponsive to a wide variety of drugs, diets and different balloon strategies (4). Consequently, new devices for transluminal revascularization have been developed and tested in clinical practice with the aim of reducing the incidence of restenosis (5–8). Intracoronary stent implantation has proved to be successful in the treatment of coronary artery dissections and in preventing abrupt vessel closure (9,10). Furthermore, it has been suggested that stenting may improve long-term angiographic outcome by optimizing the immediate angiographic result (11,12). Recently, two major randomized studies comparing balloon angioplasty with elective coronary Palmaz-Schatz stenting in de novo lesions of patients with stable angina syndromes have been completed (13,14). Both studies have demonstrated a lower rate of restenosis 7 months after the intervention in stented lesions. The Benestent trial has also shown a superior clinical outcome at 7-month follow-up in those patients who received a stent (13). Despite this real benefit, the limitations of coronary stenting, such as bleeding and vascular complications, subacute stent thrombosis and cost remain a concern for those considering stenting in their daily interventional practice. More important, the question of whether the stent is capable of reducing and not merely delaying the restenotic process needs to be addressed (15). To address this question, we assessed the 1-year clinical outcome of the 516 patients recruited in the Benestent trial.

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Address for correspondence: Dr. Patrick W. Serruys, Catheterization Laboratory, Thorax Center, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

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Methods

Study patients. Patients with stable angina and a single new lesion of the native coronary circulation were included in the study. Angiographic criteria for enrollment included a target lesion <15 mm long, located in a vessel >3 mm in diameter and supplying normally functioning myocardium. Angiographic exclusion criteria included ostial and bifurcation lesions, evidence of intracoronary thrombus, previously grafted vessels and severe vessel tortuosity. Other clinical exclusion criteria were age <30 or >75 years, contraindication to anticoagulant or antiplatelet therapy, ineligibility for coronary bypass surgery and any surgical intervention planned for the following 6 months. After providing verbal or written informed consent, patients telephoned a central office and were randomly assigned to either stent implantation or balloon angioplasty. Randomization was stratified according to center with blocks of six treatment assignments to ensure an equal distribution of treatments in each center. Clinical and angiographic characteristics of the study patients are shown in Table 1.

Angioplasty procedure. Balloon angioplasty and stent implantation were performed according to standard clinical practice (13). The articulated Palmaz-Schatz stent (Johnson & Johnson Interventional Systems) was used. Details of design and placement technique of the Palmaz-Schatz coronary stent have previously been described (13,16). All patients received aspirin (250 to 500 mg daily) and dipyridamole (75 mg three times a day) at least from the day before to 6 months after intervention. Patients undergoing coronary stent implantation were treated with a continuous infusion of dextran (1,000 ml over 6 to 8 h) and a 10,000-U bolus of unfractionated heparin at the commencement of the procedure. A heparin bolus was repeated hourly in the event of a prolonged procedure. The femoral sheaths were removed 6 to 8 h after the intervention. Oral anticoagulant therapy (warfarin) was started after sheath removal, and patients were kept on continuous intravenous heparin therapy (to maintain activated partial thromboplastin time between 60 and 90 s) for at least 36 h, until the prothrombin time had reached the therapeutic range (international normalized ratio 2.5 to 3.5). Warfarin therapy was continued for 3 months. Patients who underwent conventional balloon angioplasty received a 10,000-U bolus of unfractionated heparin followed by an additional bolus hourly if necessary. In addition, both treatment groups received calcium antagonists until hospital discharge, with further medical treatment left to the clinician's judgment.

Clinical follow-up. According to the original protocol, patients were seen in the outpatient clinic 1, 3 and 6 months after the procedure. An interview, physical examination and electrocardiography were performed. Exercise testing was performed immediately before the 6-month follow-up coronary angiogram unless early restudy had been clinically indicated. One year after the procedure, clinical information was obtained directly from the patient at the outpatient clinic, by telephone interview or from the referring physician. At this time, a questionnaire was completed and included the following information: occurrence and date of any primary clinical end point, angina status according to the Canadian Cardiovascular Society classification (17) and antianginal medication used.

Primary clinical end points. The following clinical end points were included and ranked according to the most severe on the following scale: death, cerebrovascular accident, myocardial infarction, bypass surgery or a second percutaneous intervention involving the site of the previously treated lesion. All events were reviewed by the critical events committee, which was unaware of the treatment allocation. When more than one clinical end point occurred in a patient, the event

Table 1. Baseline Clinical, Angiographic and Procedural Characteristics of 516 Patients Included in 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
Male gender	212 (82)	207 (80)
Ever-smoked	124 (48)	119 (46)
Current smoker	60 (23)	62 (24)
Diabetes mellitus	16 (6)	17 (7)
Previous conditions		
MI	48 (19)	52 (20)
CABG	5 (2)	0
Angioplasty	8 (3)	5 (2)
Hypertension	80 (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)
Artery dilated		
RCA	72 (28)	60 (23)
LAD	159 (62)	165 (64)
LCx	26 (10)	34 (13)
Type of lesion		
Concentric	118 (46)	130 (50)
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)
Nominal size of stent or balloon (mm)	3.29 ± 0.38	3.31 ± 0.34
Largest balloon size (mm)	3.30 ± 0.38	3.40 ± 0.40
Total inflation time (s)	399 ± 359	180 ± 178

Data presented are from Serruys et al. (13) and are mean value ± SD or number (%) of patients. CABG = coronary bypass graft surgery; CCS = Canadian Cardiovascular Society; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery; TIMI = Thrombolysis in Myocardial Infarction.

occurring first was considered for survival analysis. All events were considered for composite analysis.

All deaths were included for analysis regardless of cause. *Cerebrovascular accidents* occurring in patients receiving anticoagulant therapy were considered to be intracranial hemorrhages unless unequivocally demonstrated otherwise. A *myocardial infarction* was diagnosed if new pathologic Q waves according to the Minnesota Code (18) or an increase in serum creatine kinase levels to more than twice the normal value together, with an increase in the myocardial isoenzyme levels, was demonstrated. *Bypass surgery* was defined to include an emergency or elective bypass operation involving the previously treated coronary segment. *An emergency bypass operation* was defined as one that required immediate transfer of the patient from the angioplasty suite to the operating room. *Rescue stent implantation* was defined as stent deployment in the event of a complete or critical reduction in coronary blood flow (Thrombolysis in Myocardial Infarction [TIMI] grade 0 or 1) after balloon angioplasty or a reduction in baseline flow by one grade of the TIMI classification (19). In all instances, prolonged balloon inflation was attempted before rescue stenting was considered. Rescue stenting is currently perceived as an integral part of angioplasty strategy, and only associated untoward clinical events were counted as primary end points. *Second percutaneous interventions* were those involving the previously treated lesion. The initial intervention was considered complete when the guiding catheter was removed from the arterial sheath. The symptomatic indication for a second intervention was substantiated by electrocardiographic or scintigraphic evidence of myocardial ischemia, or both. *Revascularization* (surgical or percutaneous) involving other coronary artery sites was not considered a primary end point.

Secondary clinical end points. Secondary end points were assessed at the time of follow-up regardless of occurrence of primary end points and included functional angina class and antianginal medication taken at that time.

Statistical analysis. The principal clinical analysis consisted of a single comparison between the two study groups (stent and balloon) with respect to primary clinical end points regardless of the time of event occurrence. This analysis included all patients according to the intention to treat principle. The chi-square test with the Yates correction was used to compare proportions. Discrete variables are expressed as counts and percentages and were compared in terms of relative risks for stented lesions compared with balloon-dilated lesions, including 95% confidence intervals calculated by the method of Greenland and Robins (20). Event-free survival after stent placement or balloon angioplasty was determined by Kaplan-Meier techniques and displayed as survival curves. Comparison between curves was performed using the log-rank and Wilcoxon test.

Results

Baseline characteristics, procedural factors and immediate and 7-month clinical and angiographic follow-up results of the Benestent study have previously been reported (13). There were no differences in baseline clinical and angiographic characteristics between the two study groups (Table 1). Of the 259 patients randomly assigned to receive a stent, the procedure was unsuccessful in 10 (8 underwent bypass surgery, 2 were treated medically), and 14 patients (5.4%) crossed over and were treated successfully by balloon angioplasty. Of the 257 patients randomly assigned to balloon angioplasty, 11 (4.3%) crossed over and were treated successfully with the implantation of a stent, and 5 required bypass surgery. Therefore, the procedural success rates were 92.7% in patients randomly assigned to stent implantation and 91.1% in patients assigned to balloon angioplasty, whereas the angiographic success rates were 96.9% in stented lesions and 98.1% in balloon dilated lesions. Analysis of clinical outcome was performed according to the intention to treat principle, comparing follow-up of the 259 patients randomly assigned to stent implantation with that of the 257 patients randomly assigned to balloon angioplasty.

The ranking and total number of clinical events occurring in hospital are shown in Table 2. There were no differences in the incidence of any primary clinical event between the groups, and the composite rate for all in-hospital events was similar in both (16 events [6.2%] in the angioplasty group vs. 18 events [6.9%] in the stent group; relative risk [RR] 1.12, 95% confidence interval [CI] 0.58 to 2.14). Angiographically documented stent thrombosis during the hospital stay occurred in 3.5% of patients, an incidence similar to that of subacute vessel closure after balloon angioplasty (2.7%). However, the incidence of bleeding and vascular complications was significantly higher after stent implantation than after balloon angioplasty (13.5% vs. 3.1%, RR 4.34, 95% CI 2.05 to 9.18, $p = 0.001$). The mean ($\pm$SD) hospital stay was 8.5 $\pm$ 6.8 days in the stent group and significantly lower at 3.1 $\pm$ 3.3 days in the angioplasty group ($p = 0.001$).

After 7 months of follow-up, a primary clinical end point was reached by 76 (29.6%) of the 257 patients randomly assigned to balloon and by 52 (20.1%) of the 259 assigned to stent implantation (RR 0.68, 95% CI 0.50 to 0.92, $p = 0.02$). The need for a repeat angioplasty involving the target lesion was twofold higher in the balloon group than in the stent group (53 patients [20.6%] vs. 26 patients [10%], respectively; RR 0.49, 95% CI 0.31 to 0.75, $p = 0.001$). In accordance with these clinical data, the minimal lumen diameter at angiographic follow-up was greater after stent implantation than after balloon angioplasty (1.82 $\pm$ 0.64 vs. 1.73 $\pm$ 0.55 mm, $p = 0.09$, median difference 0.17 mm), and the incidence of restenosis at 7 months, according to the >50% stenosis criterion, was 22% after stent implantation compared to 32% after balloon angioplasty ($p = 0.02$).

One-year follow-up. One year after the initial intervention, clinical follow-up information was available in all but one patient from the stent group (99.8%). The mean follow-up period was 12 months (range 0.3 to 34). All interviews were performed at least 1 year after the intervention unless the patient had died in the intervening period. In 169 patients

Table 2. Frequency of Primary Clinical End Points In-Hospital and at 7 Months and 1 Year in Descending Order of Severity and Followed by Total Number of Events

Event	Angioplasty (n = 257)	Stent (n = 259)	Relative Risk (95% CI)
Death			
In-hospital	0	0	—
At 7 mo	1 (0.4)	2 (0.8)	1.98 (0.18–21.75)
At 1 yr	2 (0.8)	3 (1.2)	1.49 (0.25–8.83)
All events	2 (0.8)	3 (1.2)	1.49 (0.25–8.83)
CVA			
In-hospital	1 (0.4)	0	—
At 7 mo	2 (0.8)	0	—
At 1 yr	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)
At 1 yr	5 (1.9)	9 (3.5)	1.79 (0.61–5.26)
All events	6 (2.3)	10 (3.9)	1.65 (0.61–4.40)
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)
At 1 yr	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)
At 1 yr	4 (1.6)	5 (1.9)	1.24 (0.34–4.57)
All events	5 (1.9)	6 (2.3)	1.19 (0.37–3.05)
Elective CABG			
In-hospital	0	3 (1.2)	—
At 7 mo	6 (2.3)	8 (3.1)	1.32 (0.47–3.76)
At 1 yr	9 (3.5)	13 (5.0)	1.43 (0.62–3.29)
All events	10 (3.9)	15 (5.8)	1.49 (0.68–3.25)
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)
At 1 yr	53 (20.6)	26 (10.0)	0.49 (0.31–0.75)
All events	69 (26.8)	45 (17.8)	0.65 (0.46–0.90)
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)
At 1 yr	81 (31.5)	60 (23.2)	0.74 (0.55–0.98)
All events	100 (38.9)	83 (32.0)	0.82 (0.65–1.04)

All events = nonhierarchic listing of events at 1 year (e.g., if a patient required repeat angioplasty and later coronary artery bypass graft surgery [CABG], the total count at 1 year would reflect both events, not just the worst event that occurred); CI = confidence interval; CVA = cerebrovascular accident; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; — = not applicable.

(33%), information was obtained directly by interview, by telephone in 256 (50%) and from the referring physician in the remaining 87 (17%). After 1 year of follow-up, 176 patients (68.5%) assigned to balloon angioplasty and 199 (76.8%) assigned to stent implantation were free of clinical events ($p < 0.04$). The difference in long-term clinical outcome is displayed in the cumulative distribution curves for the primary clinical end points in both treatment groups in Figure 1. When repeat

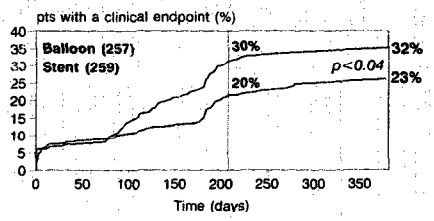

Figure 1. Cumulative frequency distribution curve for the two study groups showing percent of patients with primary clinical end points at follow-up. Significant differences in the incidence of major clinical events appearing in the first 6 months are maintained at 1-year follow-up.

intervention was removed as a primary clinical end point, there was no significant difference in 1-year event-free survival (87% for stent group, 89% for balloon group). Ranking for primary events and the total count of events at 1 year of follow-up are presented in Table 2. A primary clinical end point occurred in 81 (32%) of the 257 patients randomly assigned to balloon angioplasty and in 60 (23%) of the 259 randomly assigned to stent implantation (RR 0.74, 95% CI 0.55 to 0.98, $p = 0.04$). The most striking difference in clinical outcome between the balloon and stent groups was a significantly reduced requirement for a further percutaneous intervention to the target lesion in the latter group (21% vs. 10%, respectively, RR 0.49, 95% CI 0.31 to 0.75, $p = 0.001$). The distribution of angina class at the time of follow-up was similar in both groups, with 86% of patients in the balloon group and 82% in the stent group remaining angina-free (Table 3). Antianginal medication taken at the time of follow-up was similar in both groups (calcium antagonists 46% vs. 37%, beta-adrenergic blocking agents 31% vs. 25%, nitrates 16% vs. 13% and aspirin 88% vs. 91%, for the balloon and stent group patients, respectively). However, as we have shown, those patients who underwent balloon angioplasty required a repeat interventional procedure more frequently to remain symptom-free.

One-year status of patients event-free at 7-month follow-up. Primary clinical end points occurring after the 7-month follow-up assessment were rare. Of the 388 patients free of a primary event at 7-month follow-up, only 12 (3%) had a primary clinical event in the subsequent follow-up period.

Table 3. Functional Class 1 Year After Intervention for 516 Patients Included in Intention to Treat Analysis

CCS Functional Class	Angioplasty (n = 257)	Stent (n = 259)
No angina	218 (86)	210 (82)
I	6 (2)	16 (6)
II	23 (9)	23 (9)
III	8 (3)	4 (2)
IV	0 (0)	0 (0)
Unknown	0 (0)	3 (1)

Data are presented as number (%) of patients. CCS = Canadian Cardiovascular Society.

Table 4. Clinical and Angiographic Characteristics of Patients Who Developed a First Clinical Event After 7 Months of Follow-Up

Pt No./ Age (yr)	S/B	Primary Event	Time (mo)	Minimal Lumen Diameter (mm)		
				Post	FUP	DS% FUP
1/48	B	PTCA	7	1.91	1.22	57
2/67	S	PTCA	8	2.23	0.99	60
3/65	S	CABG	8	2.93	1.37	50
4/77	S	Q wave MI	8	2.53	2.06	34
5/55	S	PTCA	9	2.23	1.41	56
6/64	S	PTCA	11	2.30	2.77	11
7/50	S	MI	12	2.63	2.31	27
8/70	S	CABG	13	1.96	1.17	51
9/61	B	CABG	16	2.05	2.12	27
10/65	S	Q wave MI	17	2.43	2.29	31
		Death	17			
11/59	B	MI	21	2.41	2.34	49
		CABG	22			
12/57	B	PTCA	25	1.82	1.68	31

B = balloon; S = stent; DS = diameter stenosis; FUP = follow-up; Post = after procedure; Pt = patient; Time = from interventional procedure to primary clinical event.

Clinical and angiographic characteristics of these 12 patients are shown in Table 4. Of these patients, eight had undergone primary coronary stenting, and four a balloon angioplasty. The most frequent late clinical event was a revascularization procedure involving the target lesion (five repeat angioplasty, three bypass grafting). Additionally, there were three myocardial infarctions and one death. This small number of patients presenting with late clinical events does not permit a meaningful comparison between groups. However, five of the eight late revascularization procedures were performed between 7 and 11 months of follow-up, and four of these five patients had already developed angiographic restenosis at 7-month follow-up.

Discussion

The present review of the 516 patients enrolled in the Benestent trial, where patients with stable angina were randomized to stent implantation or balloon angioplasty for the treatment of new coronary lesions, demonstrates that the superior clinical outcome observed at 7-month follow-up in patients who received a stent is maintained to at least 1 year after the intervention with a low incidence of new clinical events.

Clinical outcome in balloon and stent groups. The superior clinical outcome of patients who underwent stent implantation is supported by the larger minimal lumen diameter documented at 7-month follow-up with a subsequent reduction in clinically significant restenosis (13). However, it has been suggested (15) that the stent, a permanent metallic implant incorporated into the vessel wall, could prolong the time course over which intimal hyperplasia occurs and therefore delay the appearance of restenosis to beyond the traditionally accepted period of 6 months. The results of our study show that the benefits obtained from stent implantation in the first 7 months are maintained at least to beyond the first year of follow-up, with no further increase in late (>7 months) primary events in stent group patients compared with balloon group patients. There is thus no evidence to suggest a delay in the restenosis process. It has been argued (21–23) that clinical events occurring 1 year after coronary interventions may most likely be related to the natural progression of atherosclerotic disease rather than to a delayed restenotic response to angioplasty-mediated arterial injury. Long-term angiographic follow-up studies (23) have shown a very low incidence (3%) of late stenosis at exactly the same site of previously dilated coronary segments in patients with a second coronary angiogram because of a recurrence of symptoms (23).

Our results are also supported by nonrandomized angiographic late follow-up studies (24–26). Clinical events in the 300 stent group patients included death in 0.7%, myocardial infarction in 3.7%, bypass grafting in 8% and repeat angioplasty in 13%. Eighty percent of stent group patients were free of an adverse event (24). In addition, follow-up data for the National Heart, Lung and Blood Institute–funded New Approaches in Coronary Intervention registry are being collected. However, the lack of a comparison group of patients with similar lesions treated by conventional balloon angioplasty remains an important limitation of this type of registry (25). Kimura et al. (26) reported a significantly smaller vessel diameter at 6 months than immediately after stenting in 177 patients (2.96 ± 0.41 vs. 2.32 ± 0.51 mm, respectively, $p = 0.001$), with no further decline in minimal lumen diameter between the 6- and 12-month follow-up angiogram (2.32 ± 0.51 vs. 2.30 ± 0.54 mm, respectively, p = NS). Late restenosis was documented in only four lesions (2.3%). Additionally, a

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recent preliminary report from this group (27) and that of Foley et al. (28) have shown a significant late increase in minimal lumen diameter 2 to 3 years after Palmaz-Schatz coronary stenting, suggesting favorable wall remodeling of these stented segments.

Early (<7 months) versus late (>7 months) clinical outcome. The occurrence of a first primary end point beyond 7 months after the procedure was very low in our study patients (2.3%), and although the small number of patients does not allow statistical comparison, it is of interest that most late events were revascularization procedures involving the target lesion (eight events) and that most revascularization procedures were performed close to the 7-month follow-up time in patients who had already developed restenosis at the time of angiographic follow-up (five events), suggesting that these "early" late events were in fact a consequence of a restenosis developing in the initial 7 months of follow-up. We suggest that by 7 months the adverse processes related to stent implantation, namely thrombotic occlusion and intimal hyperplasia, have become manifest, and late clinical events are more likely to be related to the natural progression of the underlying atherosclerotic disease than to the device used at the time of coronary angioplasty.

When we exclude further coronary angioplasty as a major complication, an event that can be argued is a more benign complication than death, stroke, myocardial infarction or bypass surgery, we observe no significant difference in 1-year outcome in the two treatment groups. However, it should not be forgotten that the coronary angioplasty procedure retains a small risk of mortality and morbidity. Additionally, there is a significant psychosocial impact on the patient and his or her family with every hospital admission, albeit for a "benign" procedure. The economic benefit of stenting will be investigated prospectively in the Benestent II study. It has been suggested that the cost of the stent, which, without doubt, impacts significantly on the cost of the stenting procedure, compared with balloon angioplasty, will diminish as competition for the stent market increases.

Clinical implications and conclusions. The excellent long-term survival after elective percutaneous interventions in our study is not surprising because most patients had single-vessel disease and good left ventricular function, features known to be associated with an excellent long-term prognosis. Coronary angioplasty has been demonstrated (29) to be more successful in relieving angina pectoris and improving exercise tolerance than medical treatment in patients with stable single-vessel coronary artery disease. However, the results of angioplasty are hampered by a high incidence of restenosis (30% to 40%) after an initially successful balloon dilation (30). Elective coronary stenting has been shown to improve the clinical and angiographic results of coronary angioplasty (13,14). However, these benefits are partially negated by the cost related to the stent itself, bleeding complications and a prolonged hospital stay (31,32). We eagerly await the results of trials of new stent designs, deployment strategies and adjuvant therapies in an attempt to reduce or abolish these nondesirable effects (33,34). The maintenance of the clinical benefit achieved by elective coronary stenting resulting in a diminished need for repeat procedures may help to balance the cost/benefit equation of this new interventional strategy.

Appendix

Principal Investigators and Participating Institutions for the Benestent Trial

Spain: *Carlos Macaya, MD*, University Hospital San Carlos, Madrid.

The Netherlands: *Patrick W. Serruys, MD, Peter Ruygrok, MD, Marie-Angèle Morel, MSc*, University Hospital Rotterdam, Dijkzigt, Thorax Center, Rotterdam; *Harry Suryapranata, MD*, Ziekenhuis de Weezenlanden, Zwolle; *Gijs Mast, MD*, St. Antonius Ziekenhuis, Nieuwegein; *Peter den Heijer, MD*, Academisch Ziekenhuis, Groningen; *Karel Koch, MD*, Academisch Medisch Centrum, Amsterdam; *Hans Bonnier, MD*, Catharina Ziekenhuis, Eindhoven.

Italy: *Silvio Klugmann, MD*, Hospital Maggiore, Trieste.

Switzerland: *Phillipe Urban, MD*, Hôpital Cantonal Universitaire, Geneva.

Germany: *Rudiger Simon, MD*, Christian Albrechts University, Kiel.

France: *Marie-Claude Morice, MD*, Centre Cardiologique du Nord, Paris; *Nicolas Danchin, MD*, CHUR, Nancy; *Claude Bourdonnec, MD*, Polyclinique Volney, Rennes.

Ireland: *Peter Crean, MD*, James Hospital, Dublin.

Belgium: *William Wijns, MD*, Cliniques Universitaires St. Luc, Université Catholique de Louvain, Brussels.

References

1. Holmes DR, Vliestra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung and Blood Institute. Am J Cardiol 1984;53:77C–81C.
2. Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3 and 4 months. Circulation 1988;77:361–71.
3. Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous transluminal coronary angioplasty: serial angiographic follow-up of 220 patients. J Am Coll Cardiol 1988;12:616–23.
4. Popma JJ, Califf RM, Topol EJ. Clinical trials of restenosis after coronary angioplasty. Circulation 1991;84:1426–36.
5. Bittl JA, Sanborn TA, Tebeng JE, Siegel RM, Ellis SG. Clinical success, complications and restenosis rates with excimer laser coronary angioplasty. Am J Cardiol 1992;70:1533–9.
6. Topol EJ, Leya F, Pinkerton CA, et al. A comparison of directional atherectomy with coronary angioplasty in patients with coronary artery disease. N Engl J Med 1993;329:221–7.
7. Adelman AG, Cohen EA, Kimball BP, et al. A comparison of directional atherectomy with balloon angioplasty for lesions of the left anterior descending coronary artery. N Engl J Med 1993;329:228–33.
8. Safian RD, Niazi KA, Stezelecki M, et al. Detailed angiographic analysis of high-speed mechanical rotational atherectomy in human coronary arteries. Circulation 1993;88:961–8.
9. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stent to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316:701–6.
10. Roubin GS, Cannon AD, Agrawal SK, et al. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation 1992;85:916–27.
11. de Jaegere PPT, Hermans WR, Rensing BJ, Strauss BH, de Feyter PJ, Serruys PW. Matching based on quantitative coronary angiography. A surrogate for randomized studies? Comparison between stent implantation and balloon angioplasty of a native coronary artery lesion. Am Heart J 1993;125:310–9.
12. Ellis SG, Savage M, Fischman D, et al. Restenosis after placement of Palmaz-Schatz stents in native coronary arteries: initial results of a multicenter experience. Circulation 1992;86:1836–44.

13. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–95.
14. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496–501.
15. Topol E. Caveats about elective coronary stenting. N Engl J Med 1994;331: 501–2.
16. Schatz RA, Baim DS, Leon M, et al. Clinical experience with the Palmaz–Schatz coronary stent: initial results of a multicenter study. Circulation 1991;83:148–61.
17. Goldman L, Hashimoto B, Cook F, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. Circulation 1981;64:1227–34.
18. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. Circulation 1960;21: 1160–75.
19. The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial: phase 1 findings. N Engl J Med 1985;312:932–6.
20. Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 1985;41:55–68.
21. Rosing DR, Cannon R, Watson R, et al. Three year anatomic, functional and clinical follow-up after successful PTCA. J Am Coll Cardiol 1987;9:1–7.
22. Cequier A, Bonan R, Crepeau J, et al. Restenosis and progression of coronary atherosclerosis after coronary angioplasty. J Am Coll Cardiol 1988;12:409–55.
23. Ghazzal ZM, King SB III, Douglas JS, Weintraub WS. Late angiographic status of coronary angioplasty site which was <50% narrowed 4 to 12 months after successful angioplasty. Am J Cardiol 1994;73:892–4.
24. Savage MP, Fischman DL, Schatz RA, et al. Long-term angiographic and clinical outcome after implantation of a balloon-expandable stent in the native coronary circulation. J Am Coll Cardiol 1994;24:1207–12.
25. Baim DS, Kent KM, King SB III, et al. Evaluating new devices. Acute (in-hospital) results from the new approaches to coronary intervention registry. Circulation 1994;89:471–81.
26. Kimura T, Tamura T, Yojoi H, Nobuyoshi M. Long-term clinical and angiographic follow-up after placement of Palmaz-Schatz coronary stent: a single center experience. J Intervent Cardiol 1994;7:129–39.
27. Kimura T, Yokoi H, Nakagawa Y, Tamura T, Nosaka H, Nobuyoshi M. Three years quantitative angiographic follow-up after Palmaz–Schatz coronary stent implantation [abstract]. Circulation 1994;90(Pt 2):I-323.
28. Foley JB, White J, Teefy P, Brown RIG, Almond DG. Continuing luminal remodelling more than six months after stent implantation [abstract]. Circulation 1994;90(Pt 2):I-323.
29. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. N Engl J Med 1992;326:10–6.
30. de Feyter PJ, Keane D, Deckers JW, de Jaegere P. Medium and long-term outcome after coronary balloon angioplasty. Prog Cardiovasc Dis 1994;36: 385–96.
31. Cohen DJ, Breall JA, Ho KK, et al. Economics of elective coronary revascularization: comparison of costs and charges for conventional angioplasty, directional atherectomy, stenting and by-pass surgery. J Am Coll Cardiol 1993;22:1052–9.
32. Cohen DJ, Breall JA, Ho KK, et al. Evaluating the potential cost-effectiveness of stenting as a treatment for symptomatic single-vessel coronary disease: use of a decision-analytic model. Circulation 1994;89: 1859–74.
33. Nakamura S, Colombo A, Gaglione A, et al. Intracoronary ultrasound observations during stent implantation. Circulation 1994;89:2026–34.
34. Serruys PW, Emanuelsson H, Macaya C, et al. Benestent II pilot study: in-hospital results of phase 1, 2, 3 and 4 [abstract]. Eur Heart J 1995;16: p1672.