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A COMPARISON OF CORONARY-ARTERY STENTING WITH ANGIOPLASTY FOR ISOLATED STENOSIS OF THE PROXIMAL LEFT ANTERIOR DESCENDING CORONARY ARTERY

FRANCESCO VERSACI, M.D., ACHILLE GASPARDONE, M.D., M.PHIL., FABRIZIO TOMAI, M.D., FILIPPO CREA, M.D.,
LUIGI CHIARIELLO, M.D., AND PIER A. GIOFFRÈ, M.D.

ABSTRACT

Background Randomized studies have shown that the use of coronary-artery stenting as the initial treatment for coronary stenosis is associated with a lower risk of restenosis than is standard coronary angioplasty. We prospectively investigated the efficacy of these two approaches in selected patients with isolated stenosis of the proximal left anterior descending coronary artery.

Methods A total of 120 patients with isolated stenosis of the proximal left anterior descending coronary artery were randomly assigned to stent implantation or standard coronary angioplasty. The primary clinical end points were the rate of procedural success (defined as residual stenosis of less than 50 percent and the absence of death, myocardial infarction, and the need for coronary-artery bypass surgery during the hospital stay) and the rate of event-free survival (defined as freedom from death, myocardial infarction, and the recurrence of angina) at 12 months. The angiographic end point was the rate of restenosis 12 months after the procedure.

Results The two treatment groups did not differ significantly with respect to demographic, clinical, or angiographic characteristics. The rates of procedural success were similar in the two groups of patients (95 percent in the stenting group vs. 93 percent in the angioplasty group, $P=0.98$). The 12-month rates of event-free survival were 87 percent after stenting and 70 percent after angioplasty ($P=0.04$). The rates of restenosis were 19 percent after stent implantation and 40 percent after angioplasty ($P=0.02$).

Conclusions In patients with symptomatic isolated stenosis of the proximal left anterior descending coronary artery, stenting had advantages over standard coronary angioplasty in that it was associated with both a lower rate of restenosis and a better clinical outcome. (N Engl J Med 1997;336:817-22.)

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PERCUTANEOUS transluminal coronary angioplasty (PTCA) is more effective in improving symptoms, exercise performance, and the quality of life than medical treatment in patients with single-vessel coronary artery disease.^{1,2} Two recent randomized, multicenter studies of patients with single-vessel and multivessel disease have shown that primary stent implantation in large coronary arteries results in a lower risk of restenosis and less frequent need for subsequent interventions than does PTCA.^{3,4} As a consequence, stent implantation appears to be a better therapeutic option than PTCA. However, both studies enrolled a heterogeneous group of patients with different patterns of coronary artery disease, different clinical manifestations of ischemic heart disease, and different prognoses — a fact that makes it difficult to apply the results to the care of individual patients.

We carried out a prospective, randomized study comparing the efficacy of primary stent implantation with that of PTCA in the treatment of highly selected patients with symptomatic isolated stenosis of the proximal left anterior descending coronary artery.

METHODS

Selection of Patients

The study population consisted of patients with the following characteristics: typical angina pectoris, documented myocardial ischemia, or both; a newly diagnosed, isolated stenosis of the proximal portion of the left anterior descending coronary artery (defined as a reduction of more than 50 percent of the luminal diameter, as measured by quantitative computerized angiography,

From the Servizio Speciale di Diagnosi e Cura di Emodinamica, Divisione di Cardiocirurgia, Università di Roma Tor Vergata (F.V., A.G., F.T., L.C., P.A.G.); and the Istituto di Cardiologia, Università Cattolica del Sacro Cuore (F.C.) — both in Rome. Address reprint requests to Professor Gioffrè at the Servizio Speciale di Diagnosi e Cura di Emodinamica, Divisione di Cardiocirurgia, Università di Roma Tor Vergata, via Portuense 700, 00149 Rome, Italy.

extending less than 15 mm in length in a vessel more than 3 mm in diameter); and a left ventricular ejection fraction of 40 percent or more on left ventricular angiography. Exclusion criteria were a myocardial infarction within the previous month; a contraindication to oral anticoagulation, antiplatelet therapy, or both; and anatomical contraindications, including ostial lesions, major branching of the vessel within the target lesion, total occlusion, and severe tortuosity of the proximal portion of the left anterior descending coronary artery. Patients were randomly assigned to undergo either primary stent implantation or PTCA. Before randomization could be performed, a consensus that both procedures were feasible had to be reached by two physicians experienced in invasive cardiology who were not involved in the study. The study protocol was approved by the institutional ethics committee. Written, informed consent was obtained for every patient.

Clinical Evaluation

Exertional angina was classified according to the system of the Canadian Cardiovascular Society.⁵ Patients were classified as having unstable angina according to Braunwald's criteria.⁶ Patients were classified as having had a myocardial infarction if they had definite electrocardiographic changes and documentation of abnormal cardiac-enzyme levels. Conventional risk factors were examined by direct questioning of patients and by a review of hospital records, as previously described.⁷

Stent Implantation and PTCA

Both procedures were performed in the presence of a standby surgical team. Patients received aspirin (Ascriptin, Rhone-Poulenc Rorer, Milan, Italy) and diltiazem (Dilzene, Sigma-Tau, Rome) on the day before the procedure. At the beginning of the procedure, 10,000 IU of heparin was administered intraarterially; supplemental doses were then given to maintain an activated clotting time of more than 300 seconds.

Stent Implantation

A premounted stent-delivery system (Johnson & Johnson Interventional Systems, Warren, N.J.) was used after predilation in the first 40 patients. In the remaining patients, the stent was manually mounted on a balloon that matched the angiographically determined reference diameter of the lumen; a PS 153 stent was used in seven cases, a PS 104 in three, a PS 084 in one, and a PS 154A in six. All the stents were overdilated at high pressure. After the procedure, arterial and venous sheaths were removed when the activated clotting time fell to 150 seconds or less. Heparin therapy was begun again two to four hours after the removal of the cannula. Therapy with warfarin sodium (Coumadin, Dupont Merck, Wilmington, Del.) was begun within 24 hours after the procedure. Patients continued to receive heparin infusions until an international normalized ratio of 2.5 to 3.5 was achieved. After discharge, warfarin was continued for three months and aspirin and diltiazem indefinitely.

Coronary Angioplasty

Monorail balloon catheters (Advanced Cardiovascular Systems, Temecula, Calif.; Scimed, Maple Grove, Minn.; and Cordis, Miami) were used in all patients. The management of acute or threatened closure was left to the discretion of the operator, and cross-over to stent implantation was permitted in the case of abrupt or threatened closure or suboptimal results. After discharge, aspirin and diltiazem were given indefinitely.

Clinical and Angiographic Assessment

Patients were seen in the outpatient clinic at 1, 3, 6, and 12 months. The primary clinical end points were the rate of procedural success (defined as residual stenosis of less than 50 percent in the worse of two orthogonal views, as assessed by quantitative analysis, and the absence of death, myocardial infarction, and the need for

coronary-artery bypass surgery during the hospital stay) and the rate of event-free survival at 12 months (defined as freedom from death, myocardial infarction, and recurrence of angina during the follow-up period). Secondary clinical end points were the incidence of in-hospital complications at the puncture sites necessitating major interventions and the duration of the hospital stay.

Angiography was performed in two orthogonal views after the intracoronary injection of 200 μ g of nitroglycerin. In all patients, ioversol (Optiray 320, Mallinckrodt Medical, St. Louis) was used as a contrast agent. Angiographic variables were assessed before the procedure, immediately after it, and at follow-up; the same two orthogonal views were always obtained. Quantitative analysis was performed with the use of the Automatized Coronary Analysis System (Philips, Best, the Netherlands). Measurements included the minimal luminal diameter at the point of stenosis in the projection showing the greatest narrowing and the diameter of the proximal reference segment; both were measured at end-diastole. The severity of stenosis was also expressed as the percentage reduction of the internal luminal diameter as compared with the angiographically normal proximal coronary-artery reference segment. All angiograms were analyzed by two observers who were blinded to the patients' treatment assignments; measurements were highly reproducible ($r > 0.97$), and there was no significant difference between the observers ($P = 0.24$). The average of the two measurements was used for statistical analysis. Follow-up coronary angiography was performed 12 months after the initial procedure or if symptoms suggestive of coronary restenosis developed before that time. The angiographic end point was the rate of restenosis (defined as stenosis of 50 percent or more) at 12 months.

Statistical Analysis

We calculated the size of the sample necessary to achieve 80 percent statistical power at an alpha level of 0.05. The accrual goal was based on previous reports of the effects of stent implantation and PTCA on the angiographic end point (the 12-month rate of restenosis).^{3,4,8} On the basis of the assumption that 15 percent of the patients assigned to stent implantation and 40 percent of those assigned to PTCA would have restenosis, 55 patients were required in each cohort. Assuming a 10 percent dropout rate, we set a goal of 120 patients for the study.

All analyses were performed according to the intention-to-treat principle. Continuous data are expressed as means \pm SD and were compared by the unpaired Student's *t*-test. Discrete variables were compared by the Mann-Whitney *U* test. The chi-square test with a continuity correction was used to compare proportions. Differences between the groups were considered to be statistically significant when the *P* value was below 0.05. All statistical tests were two-tailed.

RESULTS

Characteristics of the Patients

Between March 1992 and July 1995, 3918 consecutive patients were referred to our hospital for coronary angiography; 1293 patients had single-vessel disease, and 120 (105 men and 15 women; mean age, 57 ± 10 years; range, 34 to 84) had stenosis of the proximal left anterior descending coronary artery that met the inclusion criteria. Sixty patients were randomly assigned to undergo stent implantation, and 60 to undergo PTCA. Four patients dropped out of the study after randomization: two patients, one assigned to stent implantation and one to PTCA, withdrew their consent before the procedure and were treated medically; the other two patients (one assigned to each group) underwent sur-

gical revascularization. There were no significant differences in base-line clinical or angiographic characteristics between the two groups (Table 1).

Early Clinical Outcomes

The success rate was similar whether patients were treated with stenting or with PTCA (95 percent vs. 93 percent, $P=0.98$). Stent implantation was successful in 55 patients. In one patient, the stent could not be deployed because the lesion could not be predilated, and in one patient the stent was deployed too close to the stenosis. Both patients were in clinically and hemodynamically stable condition and underwent successful surgical revascularization. Another patient, in whom the stent had been successfully implanted, had subacute stent thrombosis two days after the procedure and underwent coronary bypass grafting. This patient had a Q-wave myocardial infarction.

PTCA was successful in 54 patients. Two patients assigned to undergo PTCA crossed over to stent implantation; in one patient there was residual stenosis of more than 50 percent, and in the other there was clear angiographic evidence of flow-limiting dissection (grade 1 on the scale described in the Thrombolysis in Myocardial Infarction [TIMI] trial¹⁰). In two other patients PTCA was unsuccessful. In one the lesion could not be crossed with the guide wire; this patient underwent successful coronary bypass surgery two days later. The other patient underwent urgent surgical revascularization for refractory occlusion during the procedure; this patient had a non-Q-wave myocardial infarction.

The incidence of bleeding and vascular complications at the puncture sites that resulted in pseudoaneurysm was higher after stent implantation than after PTCA (7 percent vs. 0, $P=0.12$). Three patients were treated surgically, and one was treated with prolonged compression. The median hospital stay was 6.5 days (range, 3 to 26) in the stent group and 5.0 days (range, 2 to 19) in the PTCA group ($P=0.04$). Data on the in-hospital events are shown in Table 2.

Early Angiographic Results

After the procedure, patients who underwent stent implantation had a greater immediate gain in luminal diameter than those who underwent PTCA (2.0 ± 0.6 vs. 1.4 ± 0.5 mm, $P=0.001$), resulting in a greater minimal luminal diameter (2.8 ± 0.6 vs. 2.1 ± 0.5 mm, $P=0.001$) and in less severe residual stenosis (17 ± 14 percent vs. 34 ± 13 percent, $P=0.001$). Early angiographic results are shown in Table 3.

Clinical Outcomes at 12 Months

Late clinical follow-up data were available for all patients. The rate of event-free survival at 12 months was 87 percent in the stenting group and 70

TABLE 1. BASE-LINE CLINICAL AND ANGIOGRAPHIC CHARACTERISTICS OF 120 PATIENTS INCLUDED IN THE INTENTION-TO-TREAT ANALYSIS, ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	PTCA (N=60)	STENTING (N=60)
Age — yr	57±10	56±9
Male sex — no. (%)	50 (83)	55 (92)
Risk factors — no. (%)		
Current smoking	31 (52)	38 (63)
Diabetes mellitus	10 (17)	8 (13)
Hypercholesterolemia	25 (42)	24 (40)
Hypertension	20 (33)	22 (37)
Family history of ischemic heart disease	23 (38)	26 (43)
Obesity	4 (7)	9 (15)
Previous myocardial infarction — no. (%)	15 (25)	17 (28)
Exertional angina — no. (%)†	49 (82)	50 (83)
Class I	5 (8)	4 (7)
Class II	27 (45)	22 (37)
Class III	11 (18)	18 (30)
Class IV	6 (10)	6 (10)
Unstable angina — no. (%)‡	11 (18)	10 (17)
Class IIB	6 (10)	5 (8)
Class IIIB	5 (8)	5 (8)
Ejection fraction — %	54±9	52±10
Proximal reference diameter — mm	3.2±0.34	3.3±0.37
Degree of stenosis — %	78±7	77±8
Minimal luminal diameter — mm	0.70±0.25	0.74±0.28
Type of lesion — %§		
A	5	7
B	73	68
C	22	25

*Plus-minus values are means ±SD.

†Exertional angina was categorized according to the classification system of the Canadian Cardiovascular Society.⁵ Because of rounding, the percentages for the classes of exertional angina do not total the overall percentage for exertional angina.

‡Unstable angina was categorized according to the classification system of Braunwald.⁶

§Lesions were classified according to the system of the American College of Cardiology–American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures.⁹

TABLE 2. CLINICAL OUTCOMES IN THE HOSPITAL AND DURING FOLLOW-UP, ACCORDING TO TREATMENT GROUP.*

EVENT	PTCA (N=60)	STENTING (N=60)	P VALUE
In hospital			
Revascularization procedure — no. (%)	58 (97)	58 (97)	
Procedural success	54 (93)	55 (95)	0.98
Procedural failure	4 (7)	3 (5)	0.88
Vascular complication	0	4 (7)	0.12
Median hospital stay — days	5.0	6.5	0.04
At 12 months — no. (%)			
Event-free survival	42 (70)	52 (87)	0.04
Death from cardiac causes	1 (2)	1 (2)	0.30
Nonfatal infarction	2 (3)	1 (2)	0.30
Recurrence of angina	15 (25)	6 (10)	0.05

*Percentages may not sum to 100 because of rounding.

TABLE 3. PROCEDURAL CHARACTERISTICS AND INITIAL ANGIOGRAPHIC RESULTS, ACCORDING TO TREATMENT GROUP.*

VARIABLE	PTCA	STENTING	P VALUE
Balloon diameter (mm)	3.1±0.3	3.5±0.4	0.03
Maximal inflation pressure (atm)	6.0±1.7	10.1±3.2	0.001
Total duration of inflation (sec)	255±131	240±152	0.57
Postprocedural proximal reference diameter (mm)	3.2±0.3	3.3±0.4	0.27
Final stenosis (%)	34±13	17±14	0.001
Minimal luminal diameter (mm)	2.1±0.5	2.8±0.6	0.001
Immediate gain†	1.4±0.5	2.0±0.6	0.001

*Plus-minus values are means ±SD.

†Immediate gain was calculated as the minimal luminal diameter after the procedure minus the value before the procedure.

TABLE 4. ANGIOGRAPHIC OUTCOME AT 12 MONTHS, ACCORDING TO TREATMENT GROUP.*

VARIABLE	PTCA (N=46)	STENTING (N=49)	P VALUE
Proximal reference diameter (mm)	3.2±0.4	3.3±0.4	0.4
Rate of restenosis (% of patients)	40	19	0.02
Degree of stenosis (%)	45±13	34±19	0.005
Minimal luminal diameter (mm)	1.4±0.9	1.8±1.0	0.028
Loss (mm)	0.4±0.4	0.7±0.6	0.035
Net gain (mm)	1.0±0.5	1.4±0.7	0.012

*Plus-minus values are means ±SD. Loss was calculated as the minimal luminal diameter after the procedure minus the value at follow-up, and net gain as the minimal luminal diameter at follow-up minus the value before the procedure.

percent in the PTCA group ($P=0.04$) (Table 2). In the stenting group, one patient had an acute myocardial infarction two months after discharge from the hospital and died. All the remaining patients were alive at the last follow-up visit. Symptoms developed in seven patients during the 12-month follow-up period, and one of these patients had a documented non-Q-wave myocardial infarction. All seven of these patients underwent repeated angiography. One patient had progression of the disease in the circumflex coronary artery and underwent successful PTCA; five patients had restenosis at the level of the stent; and the remaining patient had total occlusion of the left anterior descending coronary artery at a point proximal to the stent. In three patients it was possible to recanalize the artery by PTCA; one patient underwent coronary bypass grafting because he declined to undergo a second PTCA procedure, and in three patients the dosage of antianginal agents was increased to control symp-

toms. Data on events during follow-up are shown in Table 2.

In the PTCA group, one patient had an anterior Q-wave myocardial infarction three months after the procedure and died. All the remaining patients were alive at the last follow-up visit. Seventeen patients became symptomatic during the 12-month follow-up period. Non-Q-wave myocardial infarction was documented in 2 of these 17 patients. The other 15 underwent repeated angiography, and all had evidence of restenosis. In six patients a stent was successfully implanted. Seven patients underwent repeated PTCA, which was successful in three. In one patient the results of PTCA were considered suboptimal; the patient underwent coronary surgery because he refused stent implantation. Three patients were treated medically with increasing dosages of antianginal drugs; one of the three declined repeated angiography. In this patient, thallium-201 scintigraphy strongly indicated exercise-induced ischemia in the territory of the left anterior descending coronary artery, thus suggesting restenosis; he was treated medically.

Angiographic Results at 12 Months

Coronary angiography was repeated at 12 months in 49 patients assigned to stenting and in 46 patients assigned to PTCA who were eligible for follow-up ($P=0.14$). All patients in whom coronary angiography was not repeated were free of symptoms. The rate of restenosis was 19 percent after stent implantation and 40 percent after PTCA ($P=0.02$). At 12 months, the stenting group had a greater mean reduction in the luminal diameter from the value immediately after the procedure ($0.7±0.6$ mm, vs. $0.4±0.4$ mm in the PTCA group, $P=0.035$) but also a greater net gain over the base-line value ($1.4±0.7$ vs. $1.0±0.5$ mm, $P=0.012$), resulting in a greater minimal luminal diameter ($1.8±1.0$ vs. $1.4±0.9$ mm, $P=0.028$). Data on the results of follow-up angiography are shown in Table 4.

DISCUSSION

Our findings indicate that in symptomatic patients with isolated stenosis of the proximal left anterior descending coronary artery, primary stent implantation, as compared with PTCA, resulted in a similar rate of immediate procedural success, superior early and late angiographic results, a more favorable clinical outcome at 12 months, and a lower 12-month rate of restenosis.

The treatment of symptomatic patients with isolated stenosis of the proximal left anterior descending coronary artery is difficult.¹¹⁻¹⁴ Epidemiologic and investigational data indicate that disease of the proximal left anterior descending coronary artery is a "high-risk" lesion because this artery supplies 40 to 50 percent of the total left ventricular myocardi-

um; thus, an occlusion at this site results in ischemia in a large portion of the myocardium.^{15,16} This high-risk stenosis can be treated medically, by PTCA, by stenting, or by surgery. The best therapeutic approach is still being debated.

In the Angioplasty Compared to Medicine Study,¹⁷ 69 of the 212 patients with single-vessel disease who were randomly assigned to PTCA or medical therapy had stenosis of the proximal left anterior descending coronary artery. After six months of follow-up, the patients who underwent PTCA had greater exercise tolerance and fewer symptoms than the medically treated patients.¹⁷

Coronary-artery bypass grafting with the left internal thoracic artery is an excellent alternative treatment for isolated stenosis of the proximal left anterior descending coronary artery.^{18,19} The Lausanne study, designed to compare PTCA and grafting with the left internal thoracic artery for the treatment of isolated stenosis of the left anterior descending coronary artery, found a similar survival rate in the two groups, but PTCA was associated with a greater risk of restenosis and more frequent need for reintervention.²⁰ A report from a recent trial in which patients were randomly assigned to surgery, PTCA, or medical therapy indicated that, among patients who underwent surgery with a graft from the left internal thoracic artery, the incidence of cardiac events during follow-up was significantly lower than among patients assigned to PTCA or medical treatment.²¹

Recent randomized, prospective, multicenter studies have shown that in patients with coronary artery disease, primary stent implantation, on average, is associated with a lower incidence of restenosis, defined both angiographically and clinically, than PTCA.^{3,4} Furthermore, a retrospective analysis of the Stent Restenosis Study showed that although stenting, as compared with PTCA, provided a better average net gain in luminal diameter, the gain was greater in patients who had stents implanted in the left anterior descending coronary artery than in patients who had stents implanted in other coronary arteries.²² On the basis of these data, we postulated that primary stent implantation for the treatment of isolated stenosis of the proximal left anterior descending coronary artery could be a better therapeutic option than PTCA.

In this study, primary stent implantation resulted in a better long-term angiographic and clinical outcome than PTCA, mainly because of a reduced need for additional interventions. After 12 months of follow-up, 87 percent of the patients treated with stenting, as compared with 70 percent of those treated with PTCA, were asymptomatic and free of cardiac events (defined as death, myocardial infarction, and recurrence of angina). The greater clinical benefit in patients treated with stenting is unlikely to be due to anticoagulant therapy, since previous studies have

shown that anticoagulation does not improve the clinical outcome after PTCA.^{23,24}

In contrast to previous studies in which very heterogeneous groups of patients were randomly assigned to stenting or PTCA, our study compared the two approaches in a well-characterized cohort of symptomatic patients who had reasonably good left ventricular function and isolated stenosis of the proximal left anterior descending coronary artery in a vessel at least 3 mm in diameter. Interestingly, the rate of recurrence of angina after one year of follow-up was similar to that observed in the Benestent trial, which enrolled a much more heterogeneous group of patients.²⁵

The incidence of major peripheral vascular complications was higher in the stenting group than in the PTCA group in our study. Furthermore, the duration of hospitalization was longer for the patients treated with stenting than for those treated with PTCA, confirming a previous report from other European institutions.²⁶ However, in the present study we used a very aggressive antithrombotic and anticoagulant regimen. It is likely that by using an antithrombotic regimen only, as recently proposed, the incidence of peripheral complications and the hospital stay could be significantly reduced without affecting the long-term patency of the stented vessel.^{26,27} The hospital stay in our study was, on average, longer than that reported in the United States.⁴ This difference is probably due to a longer time lag in our hospital between admission and the revascularization procedure.

Clinical follow-up was based only on the clinical examination, electrocardiography at rest, and the interview. We did not systematically perform noninvasive testing to assess functional capacity objectively. Moreover, although primary stent implantation, as compared with PTCA, resulted in a more favorable clinical outcome at 12 months, our study did not show a significant difference between the groups in mortality due to cardiac causes. This could be due to the low rate of mortality among patients with single-vessel disease and good left ventricular function, the small number of patients studied, the short duration of follow-up, or a combination of these factors.¹³

In symptomatic patients with isolated, uncomplicated stenosis of the proximal left anterior descending coronary artery in a vessel at least 3 mm in diameter, primary stent implantation, as compared with PTCA, resulted in better immediate and late angiographic results, reduced the incidence of restenosis, and was associated with a more favorable clinical outcome at 12 months. Since this study showed that in highly selected patients with isolated disease of the proximal left anterior descending coronary artery, primary stent implantation resulted in a better long-term outcome than PTCA, a comparison of the results of stenting with those of the best surgical therapy is now warranted.

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