INTERVENTIONAL CARDIOLOGY AND SURGERY

A comparison of coronary artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery: five year clinical follow up

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Background: Stent implantation for isolated stenosis of the proximal left anterior descending coronary artery (LAD) with preserved left ventricular function has been found to have a better clinical and angiographic outcome at one year than balloon angioplasty (PTCA).

Objective: To establish whether those results are maintained at five year follow up.

Methods: Patients were followed at least every six months. For those who died during follow up, data were obtained from medical records.

Main outcome measures: Freedom from death, non-fatal myocardial infarction, cerebrovascular accident, and repeated target lesion revascularisation. Secondary end points were revascularisation in a remote region and freedom from angina.

Results: Follow up was complete in all patients. At five years, the primary end point was reached more often by patients randomised to stent implantation than to PTCA (80% v 53%; odds ratio (OR) 0.29 (95% confidence interval (CI) 0.13 to 0.69); $p = 0.0034$). In the PTCA group, 35% of patients underwent target lesion revascularisation v 15% in the stent group (OR 0.33, 95% CI 0.13 to 0.80; $p = 0.014$). There was a trend towards increased mortality in the PTCA group than in the stent group (17% v 7%; OR 0.36, 95% CI 0.10 to 1.21; $p = 0.098$). No significant differences were found between PTCA and stent groups for non-fatal myocardial infarction (8% v 5%; OR 0.58, 95% CI 0.13 to 2.54; $p = 0.46$) or cerebrovascular accident (2% v 0%).

Conclusions: In patients with isolated stenosis of the proximal LAD, a five year clinical follow up confirmed a better outcome in those treated with stenting than with PTCA.

In a previous randomised prospective study, we showed that in patients with symptomatic isolated stenosis of the proximal left anterior descending coronary artery (LAD), those randomised to stent implantation had a better one year clinical and angiographic outcome than those randomised to percutaneous transluminal coronary angioplasty (PTCA).¹

Our aim in the present study was to establish whether the early favourable results observed in the randomised one year study are maintained at a five year follow up.

METHODS

Study patients

The study population consisted of patients with the following characteristics: typical angina pectoris, documented myocardial ischaemia, or both; a newly diagnosed isolated stenosis of the proximal portion of the LAD (defined as a reduction of more than 50% in luminal diameter as measured by quantitative computed angiography, extending less than 15 mm in length in a vessel of more than 3 mm in diameter); and a left ventricular ejection fraction of 40% or more on left ventricular angiography. Exclusion criteria were a myocardial infarct within the previous month; contraindication to oral anticoagulation or 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 LAD.

Eligible patients were randomised to either Palmaz-Schatz stent implantation or balloon angioplasty. In all, 120 patients were included: 60 in the balloon group and 60 in the stent

group. Clinical and angiographic characteristics were described previously¹ and are summarised in table 1.

Procedures

The procedural technique was described in our previous report.¹ All patients received aspirin and diltiazem the day before the procedure and a 10 000 IU bolus of heparin at the beginning of the procedure. In patients undergoing stent implantation, heparin treatment was begun again 2-4 hours after the removal of the sheaths. Treatment with warfarin sodium was started within 24 hours after the procedure. Patients continued to receive heparin infusions until an international normalised ratio of 2.5 to 3.5 was achieved. Warfarin was continued for three months.

After discharge, all patients received aspirin and diltiazem indefinitely.

Follow up

Patients were seen in the outpatient clinic every six months up to five years, or earlier in case of recurrence of symptoms. For patients who died during follow up, data were obtained from their medical records. The primary clinical end point was the rate of event-free survival at five years, defined as freedom from death, cerebrovascular accident, non-fatal myocardial infarction, and target lesion revascularisation. Secondary end points were exertional angina class, need for revascularisation of a remote myocardial region, and current drug treatment.

All clinical events were verified by an independent clinical committee. When more than one clinical end point occurred

Table 1 Baseline angina characteristics of 120 patients included in intention to treat analysis, according to treatment group

	Angioplasty (n = 60)		Stent (n = 60)		p Value
	n	%	n	%	
Exertional angina	49	82	50	83	0.79
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	11	18	10	17	
Class IIb	6	10	5	8	
Class IIIb	5	8	5	8	

in a patient, only the first event was counted for survival analysis.

Statistical analysis

Normally distributed variables are expressed as mean (SD) and were compared using the unpaired Student *t* test. A χ^2 test with continuity correction was used to compare proportions. All statistical tests were two tailed. Discrete variables are expressed as percentages and were compared in terms of odds ratio (OR) for stented lesions *v* balloon dilated lesions, including 95% confidence intervals (CI) calculated by the χ^2 method and Fisher's exact test. Differences between the groups were considered significant when the probability value was $p < 0.05$. Time to first event-free survival after stent implantation or balloon angioplasty was determined by the Kaplan–Meier method and displayed as survival curves. Comparison between curves was carried out using the Cox proportional hazard regression analysis. All statistical analysis was done using Statview (version 5.0) for Windows (SAS Institute Inc).

RESULTS

In-hospital outcome and one year follow up

As previously reported,¹ there were no significant differences in baseline clinical or angiographic characteristics between the two groups. Acute angiographic and procedural success rates were similar in the two groups (two patients in the PTCA group crossed over into the stent group because of a residual stenosis of $> 50\%$ and angiographic evidence of flow limiting dissection). There was no difference in the incidence of major clinical events between the groups during the hospital stay. No patient had cerebrovascular complications. At one year, a primary clinical end point was reached in 65% of the patients in the PTCA group compared with 85% of those in the stent group (OR 0.33, 95% CI 0.13 to 0.81; $p = 0.0179$).¹ The rates of restenosis and target lesion revascularisation were increased in the PTCA group compared with the stent group (40% *v* 19%, $p = 0.02$; and 32% *v* 10%, $p = 0.0053$, respectively). No differences in mortality (2% *v* 2%) or non-fatal myocardial infarction (5% *v* 3%) were observed between the two groups.

Five year follow up

Primary and secondary clinical end points are detailed in tables 2, 3, and 4. All patients enrolled in the study completed the five year follow up. The prevalence of risk factors was similar in patients undergoing PTCA and stent implantation both at baseline and at the five year follow up. Furthermore, the use of β blockers, nitrates, and statins was similar between the groups. Of the 60 patients randomised to stent implantation, 48 (80%) were free of major adverse cardiac events, compared with 32 of the 60 patients (53%)

randomised to PTCA (OR 0.29, 95% CI 0.13 to 0.69; $p = 0.0034$) (fig 1).

A trend towards a higher total and cardiac mortality was observed in patients treated with PTCA than in those treated with stenting (17% *v* 7%; OR 0.36, 95% CI 0.10 to 1.21, $p = 0.098$; and 13% *v* 5%; OR 0.34, 95% CI 0.08 to 1.36, $p = 0.12$, respectively). There were two additional cases of target lesion revascularisation in the PTCA group (3%) versus three (5%) in the stent group ($p = 0.99$) (fig 2). No angiographically significant new lesions in the LAD requiring interventional treatment were observed in our patients at follow up. At the five year follow up, 26 patients in the PTCA group (52%) *v* 41 (73%) in the stent group were free of angina (OR 0.32, 95% CI 0.14 to 0.75; $p = 0.075$). The need for new revascularisation in a remote region did not differ between groups (5% *v* 8%; $p = 0.46$); in particular, it was similar in the diabetic patients in the two groups: one in the stent group and two in the PTCA group (2% *v* 3%; $p = 0.99$).

DISCUSSION

Our findings indicate that in symptomatic patients with isolated proximal stenosis of the LAD and preserved left ventricular function, primary stent implantation resulted in a more favourable clinical outcome than PTCA at five years, confirming a persistent benefit of stent implantation over PTCA beyond the first 12 months.

Figure 1 Kaplan-Meier event-free survival curves (defined as freedom from death, myocardial infarction, cerebrovascular accident, and target lesion revascularisation) of the two study groups at the five year follow up. At one year, the primary clinical end point was reached in 85% of the patients randomised to stent implantation (solid line) and in 65% of the patients randomised to PTCA (dashed line). The difference in the overall incidence of the primary end point, which was significant at one year, maintained its significance at five years (80% in the stent group *v* 53% in the PTCA group, $p = 0.0034$).

Table 2 Primary clinical end points

	Angioplasty (n = 60)		Stent (n = 60)		p Value	OR	95% CI
	n	%	n	%			
<i>Event-free survival</i>							
1 to 12 months	39	65	51	85	0.0179	0.33	0.13 to 0.81
13 to 60 months	32	53	48	80	0.0034	0.29	0.13 to 0.69
<i>All causes of death</i>							
1 to 12 months	1	2	1	2	0.99		
13 to 60 months	9	15	3	5	0.08		
Total	10	17	4	7	0.098	0.36	0.10 to 1.21
<i>Cardiac death</i>							
1–12 month	1	2	1	2	0.99		
13–60 month	7	12	2	3	0.10		
Total	8	13	3	5	0.12	0.34	0.08 to 1.36
<i>Non-cardiac death</i>	2*	3	1†	2	0.99		
<i>Non-fatal AMI</i>							
1–12 months	3	5	2	3	0.99		
13–60 months	2	3	1	2	0.99		
Total	5	8	3	5	0.46	0.58	0.13 to 2.54
<i>CVA</i>							
1–12 months	0	0	0	0			
13–60 months	1	2	0	0	0.99		
Total	1	2	0	0	0.99		
<i>TLR</i>							
1–12 months	19	32	6	10	0.0053		
13–60 months	2	3	3	5	0.99		
Total	21	35	9	15	0.014	0.33	0.13 to 0.80

*Myelodysplasia; car accident.

†Colon cancer.

AMI, acute myocardial infarction; CI, confidence interval; CVA, cerebrovascular accident; OR, odds ratio; TLR, target lesion revascularisation.

So far the longest follow up of patients randomised to PTCA or stent implantation has been in the Benestent-I study.² In that study, at the five year follow up there were significant differences between PTCA and stenting for the rate of target lesion revascularisation. Disease progression in non-stented vessels accounted for the majority of late revascularisations. In addition, in a four year follow up Betriu and colleagues showed that most of the repeated procedures (84%) were carried out in the first six months.³

Long term follow up of non-randomised trials of patients treated with Palmaz-Schatz stents have confirmed that the progressive increase in repeated revascularisation over longer periods can be attributed to progression of coronary disease

at other sites rather than to late impairment of the stented vessel.^{4–6}

In our study, in the time interval between 13 months and five years after the procedure, there were only two additional cases of target lesion revascularisation in the PTCA group (3%) and three (5%) in the stent group, suggesting that the advantage of coronary stenting over PTCA is limited to the first 12 months. Moreover, after the first year, the likelihood of the disease progressing is quite low, and similar between treated and remote coronary vessels.

In our trial we found that the incidence of total and cardiovascular mortality was similar to previous studies, including patients with proximal LAD stenosis undergoing

Table 3 Secondary clinical end points (exertional angina class and drug treatments) and risk factors at the five year follow up

	Angioplasty (n = 50)		Stent (n = 56)		p Value	OR	95% CI
	n	%	n	%			
Angina class							
Asymptomatic	26	52	41	73	0.075	0.32	0.14 to 0.75
Exertional angina							
Class I	13	26	6	11			
Class II	4	8	3	5	0.13		
Class III	6	12	5	9			
Class IV	1	2	1	2			
Unstable angina	0	0	0	0			
Ejection fraction (%)*	53 (10)		56 (9)		0.16		
Current drugs							
Aspirin	48	96	53	95			
Ticlopidine	2	4	3	5			
β Blockers	18	36	18	32			
Calcium antagonists	22	44	17	30	0.11		
Nitrates	18	36	16	29			
HMG-CoA reductase	22	44	24	43			
Diuretics	3	6	4	7			
ACE inhibitors	26	52	24	43			
Diabetes mellitus	8	16	9	16	0.99		
Current smoking	9	18	8	14	0.61		

*Mean (SD).

ACE, angiotensin converting enzyme; CI, confidence interval; HMG CoA, hydroxymethylglutaryl-coenzyme A reductase; LAD, left anterior descending coronary artery; OR, odds ratio.

Table 4 Secondary clinical end points (no LAD revascularisation in overall patients)

	Angioplasty (n = 60)		Stent (n = 60)		P Value	OR	95% CI
	n	%	n	%			
1–12 months	0	0	1	2	0.99		
13–60 months	3	5	4	7	0.99		
All events	3	5	5	8	0.46	0.58	0.13 to 2.54

Figure 2 Kaplan-Meier event-free survival for target lesion revascularisation: the reduced need for target lesion revascularisation was maintained in the stent group. Between 13 months and five years after the procedure, there were two additional cases of target lesion revascularisation in the PTCA group (3%) versus three (5%) in the stent group ($p = 0.99$).

percutaneous coronary interventions. Even though we studied patients with simple LAD stenosis and preserved left ventricular function, epidemiological data indicate that patients with proximal LAD lesions are at high risk of major cardiac events, as this artery supplies 40–50% of the total left ventricular myocardium. In line with this, O’Keefe and colleagues reported a two year mortality of 5% in patients with proximal LAD stenosis who underwent PTCA,⁷ and Jones and colleagues reported a five year mortality of 13%.^{8,9} In our study, stenting resulted in a 60% reduction in cardiac mortality compared with PTCA, although this difference failed to achieve significance, probably because of the small number of patients.

Limitation of the study

Our findings should be evaluated in the light of the rapid development of new techniques for myocardial revascularisation such as off-pump coronary bypass,¹⁰ and new intracoronary prostheses such as drug eluting stents.¹¹ Also pharmacological treatment has improved with the use of new antiplatelet agents,^{12,13} statins,^{14,15} and, in some clinical settings, anti-inflammatory drugs.¹⁶ Nevertheless our findings confirm the present long term superiority of stent revascularisation over PTCA for the treatment of LAD stenosis.

Clinical implications

In symptomatic patients with isolated proximal LAD disease and preserved left ventricular function, primary stent implantation results in a more favourable long term clinical outcome than PTCA. The results of our study—in keeping with the one year data—reinforce the superiority of stenting over PTCA in high risk patients, such as those with proximal LAD stenosis. The use of adjunctive treatment in this subset

of patients is mandatory, and a comparison of the results of such treatment with the best surgical treatment is now warranted.

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