Early outcome after paclitaxel-eluting stents in patients with acute and subacute myocardial infarction. A clinical study

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Key words:
Drugs; Myocardial infarction; Stents.

Background. **Paclitaxel-eluting stents (PES) have been proven to prevent in-stent restenosis in patients submitted to elective percutaneous coronary intervention. No data are so far available about the safety and efficacy of PES in acute and subacute myocardial infarction. The aim of the present investigation was to evaluate the occurrence of in-hospital adverse events in patients with acute and subacute myocardial infarction submitted to PES implantation.**

Methods. **From June 1 to July 31, 2003, we implanted 53 PES in 43 consecutive patients with acute (34 patients) and subacute (9 patients) myocardial infarction.**

Results. **In 65.1% of the patients the culprit lesion was located in the left anterior descending artery. Direct stenting was performed in 27.9% and glycoprotein IIb/IIIa inhibitors were used in 74.4%. Before the procedure a TIMI flow 0-1 was present in 46.5% while post-procedural TIMI flow 3 was achieved in all patients. A pre-procedural TIMI thrombus grade 2 to 5 was present in 67.8%. No death, reinfarction, early post-infarction angina or any other episode referable to in-stent thrombosis were observed during hospitalization. No patient was submitted to target lesion revascularization. At short-term follow-up with a mean duration of 118 ± 75 days from discharge no cardiac or non-cardiac death, reinfarction or any other major adverse coronary events were reported in the study population and no target lesion revascularization was performed.**

Conclusions. **In this study, PES implant in patients with acute and subacute myocardial infarction was safe, with an early outcome comparable to conventional standard stents and no adverse events related to acute or subacute thrombosis.**

(Ital Heart J 2004; 5 (7): 536-540)

Received February 27, 2004; revision received May 10, 2004; accepted May 13, 2004.

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Introduction

Previous studies[1,2] showed that stent implantation improves the procedural success rate and clinical outcome compared to balloon angioplasty in patients with acute myocardial infarction (MI). However restenosis is still the most important long-term limitation of stent placement[1,2].

Rapamycin-eluting stent implantation has been shown to virtually abolish in-stent restenosis in elective patients with relatively simple[3] or more complex lesions[4] (longer lesions and small vessels). More recently, the safety of rapamycin-eluting stent has been evaluated in patients with acute coronary syndromes[5] and in patients with acute MI[6], conditions both associated with an increased risk for thrombotic complications during the first days after percutaneous coronary intervention (PCI). In both clinical settings, rapamycin-eluting stent implantation has been demonstrated to be as safe as bare metal stents in terms of subacute in-stent thrombosis. Besides, no angiographic restenosis was observed at 6 months in patients with acute MI treated with rapamycin-eluting stent.

Recent studies (TAXUS I-IV)[7-10] performed with paclitaxel-eluting stents (PES), yielded excellent results in preventing in-stent restenosis in patients submitted to elective PCI.

However, no data regarding the safety and the early outcome of patients with MI submitted to primary PCI and PES implantation have so far been published in the literature. Therefore, the aim of the present paper was to evaluate the occurrence of in-hospital adverse events in patients with acute and subacute MI submitted to PES implantation. A short-term (3 months) follow-up was also performed.

Methods

Patient population. From June 1 to July 31, 2003, we implanted 53 PES

(TAXUS™, Boston Scientific, Natick, MA, USA) in 43 consecutive patients with acute and subacute MI. No patient was excluded from the study. Acute MI was defined as typical chest pain lasting > 20 min and associated with at least 1 mm ST-segment elevation in two contiguous leads or with new complete left bundle branch block.

Thirty-four patients presenting with acute MI and ST-segment elevation were submitted to PCI within 12 hours of symptom onset, whereas 9 patients presented with a subacute MI and were submitted to PCI within 7 days of symptom onset. No thrombolytic therapy was administered to patients with acute and subacute MI before PCI.

Except for PES utilization, all procedures were performed according to standard techniques.

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates. Quantitative analysis of all angiographic data before, during and after the procedure were performed using the Medis Rotterdam System (Cardiovascular Measurement System, Medis Medical Imaging System, Nuenen, The Netherlands) by means of edge detection techniques. The lumen diameter of the coronary artery and the degree of stenosis were measured before (in patients with TIMI flow grade > 0) and after balloon dilation, and at the end of the procedure in all patients.

Angio analysis was performed by an attending physician (MC) who was unaware of the patients' history. The target lesion was defined as the stented segment plus the 5 mm segments proximal and distal to it[3]. At the end of the procedure, the correct TIMI frame count was also assessed using the technique described by Gibson et al.[11]. Angiographic evidence of thrombus in the target lesion was evaluated by means of the TIMI thrombus grade[12].

Before PCI all patients received weight-adjusted heparin to achieve an activated clotting time > 250 s or between 200 to 250 s when glycoprotein IIb/IIIa inhibitors were used. All patients who were not on antiplatelet drugs before PCI, received intravenous aspirin (500 mg), and clopidogrel (300 mg) just before the procedure. The administration of glycoprotein IIb/IIIa inhibitors just before PCI was at the operator's discretion. The post-procedural antiplatelet regimen consisted of lifelong aspirin use and 75 mg clopidogrel per day for 9 months or ticlopidine, 250 mg twice daily for 9 months if patients were pre-treated. The Local Ethics Committee approved the study protocol and informed written consent was obtained from all patients.

Definitions and follow-up. The adverse events evaluated during hospitalization included death, reinfarction, recurrent ischemia and target vessel revascularization (surgical or percutaneous reintervention motivated by an occlusion or significant stenosis located within the stent or in the 5 mm segments proximal or distal to it), vascular complications and hemorrhage. Data were collected in a dedicated database and analyzed retrospectively.

The incidence of adverse events during follow-up was evaluated by phone interview after at least 90 days from discharge.

Statistical analysis. Continuous variables are expressed as mean ± SD. Discrete variables are presented as count and percentages. The Student's t-test was performed to evaluate differences in the quantitative coronary angiography results before and after stent implantation.

Results

Table I shows the demographic and clinical characteristics and risk factors of the 43 patients included in the study. Angiographic and procedural data are depicted in table II. The assessment of coronary perfusion and evaluation of thrombosis are shown in table III. Twenty-one patients (48.8%) presented multivessel disease at angiography. In 28 patients (65.1%) the culprit lesions were located in the left anterior descending artery. Direct stenting was performed in 27.9% and in 4 patients (9.3%) mechanical thrombus aspiration was performed using Angiojet (Possis, Minneapolis, MN, USA) before PES implantation. An intra-aortic balloon pump was positioned in 2 patients (4.6%) because of hypotension and owing to the presence of an extensive

Table I. Demographic and clinical characteristics and cardiovascular anamnesis.

No. patients	43
Age (years)	61.2 ± 12
Age > 75 years	6 (14%)
Females	7 (16.3%)
Current smokers	21 (48.9%)
Former smokers	7 (16.3%)
Arterial hypertension	21 (48.9%)
Family history for CAD	16 (37.2%)
Hypercholesterolemia	15 (34.9%)
Diabetes mellitus	7 (16.3%)
Previous stable angina	2 (4.6%)
Previous unstable angina	10 (23.2%)
Previous acute MI	10 (23.2%)
Previous PCI	4 (9.3%)
Previous CABG	1 (2.3%)
Time to revascularization procedure (acute MI) (hours)	6 ± 5.9
Time to revascularization procedure (subacute MI) (hours)	60 ± 50.2
Killip class before procedure	
1	40 (93%)
2	3 (7%)

CABG = coronary artery bypass graft; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table II. Angiographic and procedural data.

Infarct-related artery	
Left anterior descending	28 (65.1%)
Left circumflex	10 (23.3%)
Right coronary	3 (7%)
Left main	1 (2.3%)
Venous graft	1 (2.3%)
No. vessels with > 75% stenosis or with occlusions	
One	22 (51.2%)
Two	11 (25.6%)
Three	10 (23.2%)
Direct stenting	12 (27.9%)
Angiojet system	4 (9.3%)
Intra-aortic balloon counterpulsation	2 (4.6%)
Glycoprotein IIb/IIIa inhibitors	32 (74.4%)

Table III. Assessment of coronary perfusion and evaluation of thrombosis.

TIMI flow before procedure (n = 43)	
0-1	20 (46.5%)
2	8 (18.6%)
3	15 (34.9%)
TIMI flow before procedure in acute MI (n = 34)	
0	14 (41.2%)
1	5 (14.2%)
2	6 (17.6%)
3	9 (26.5%)
TIMI flow before procedure in subacute MI (n = 9)	
0	1 (11.1%)
1	0
2	2 (22.2%)
3	6 (66.7%)
TIMI flow 3 after procedure	43 (100%)
Corrected TIMI frame count after procedure	
Left anterior descending	20.2 ± 5.7
Left circumflex	26.0 ± 7.9
Right coronary	16.8 ± 0
Mean value	21.19 ± 6.9
TIMI thrombus grade before procedure	
0-1	16 (37.2%)
2-4 (patients with non-occluded IRA with angiographic evidence of thrombus)	10 (23.2%)
5 (total occlusion)	17 (39.5%)

IRA = infarct-related artery; MI = myocardial infarction.

infarct area. Platelet glycoprotein IIb/IIIa inhibitors (abciximab or tirofiban) were administered preoperatively to 32 patients (74.4%). Before PCI clopidogrel (300 mg) was administered to 38 patients (88.4%) who were not on any antiplatelet regimen. Ticlopidine, 250 mg twice daily, was administered to the 5 patients who were already on this drug.

Before the procedure a TIMI flow 0-1 was present in 20 patients (46.5%) whereas a post-procedural TIMI flow 3 was achieved in all patients (Table III). The mean value of the corrected TIMI frame count assessed in the culprit vessels at the end of the procedure was 21.19 ± 6.9.

Before the procedure, a TIMI thrombus grade ≥ 2 (angiographic evidence of thrombus) was present in 12 of the 28 patients (42.8%) with an incompletely occluded infarct-related artery.

Overall, 53 PES were positioned on 53 different lesions. In particular, in 8 patients 2 PES were implanted at different sites of the infarct-related artery (overlapping in 4 cases). In 1 patient, 3 PES were deployed in the infarct-related artery because of dissection following the first stent implantation.

Table IV shows the length and diameter of the implanted stents.

Quantitative coronary analysis (MEDIS' software QCA-CMS Version 4.1 for Windows) before and after PES implantation is reported in table V.

After the procedure, manual compression at the puncture site was performed in 22 patients (51.2%) usually 1 hour after the end of glycoprotein IIb/IIIa and unfractionated heparin infusion (12-24 hours after PCI); in 20 patients (46.5%) hemostasis was obtained using the Angioseal device and in 1 patient (2.3%) using the Perclose device in the catheterization laboratory just after PCI. The mean length of hospitalization was 6.6 ± 2.2 days.

In the population included in the study, no death, reinfarction, early post-infarction angina or any other episode referable to in-stent thrombosis were observed during hospitalization. No patient was submitted to target vessel revascularization (PCI or coronary artery bypass grafting). Two patients (4.6%) presented with a hematoma requiring surgical repair at the puncture site; both patients were on clopidogrel and one had been treated with abciximab.

Follow-up data were obtained by telephone interview at a mean time of 118 ± 75 days (range 90-150 days) from hospital discharge. No cardiac or non-cardiac death, reinfarction or any other major adverse coronary events were reported.

In the considered period, no surgical or percutaneous target vessel revascularization was performed in any patient. Rehospitalization after discharge was necessary in 2 patients (4.6%), in one case for a non-infarct-related artery revascularization at elective PCI, and in the other for surgical repair of an atrioventricular right femoral fistula.

Table IV. Length and diameter of implanted stents.

Diameter (mm)	Length (mm)						
	8	12	16	20	24	28	32
2.25				1			
2.5				2	2		
2.75	1	4	2	5	3		1
3.0	1	9	8	4	3	2	3
3.5		1		1			

Table V. Results of subsegmental quantitative coronary analysis.

Variable	Proximal edge	Stented segment	Distal edge
Mean diameter (mm)			
Before procedure (TIMI flow 1-3, n = 28)	2.79 ± 0.45	1.64 ± 0.41	2.30 ± 0.51
Before stent implantation (n = 43)	2.96 ± 0.40	2.00 ± 0.42*	2.37 ± 0.47
After stent implantation (n = 43)	2.98 ± 0.43	2.79 ± 0.34*	2.52 ± 0.46
Minimal lumen diameter (mm)			
Before procedure (TIMI flow 1-3, n = 28)	2.47 ± 0.47	0.28 ± 0.20	2.04 ± 0.57
Before stent implantation (n = 43)	2.66 ± 0.43	1.23 ± 0.61*	2.13 ± 0.51
After stent implantation (n = 43)	2.71 ± 0.43	2.53 ± 0.34*	2.27 ± 0.43
Stenosis (% of lumen diameter)			
Before procedure (TIMI flow 1-3, n = 28)	5.69 ± 5.78	86.32 ± 10.14	6.11 ± 4.57
Before stent implantation (n = 43)	4.87 ± 3.54	44.14 ± 19.73*	5.31 ± 2.21
After stent implantation (n = 43)	4.84 ± 4.07	6.25 ± 2.82*	4.98 ± 3.75

* $p < 0.0001$ before vs after stent implantation in the stented segment. Non-significant differences between the proximal and distal edges.

Discussion

So far, PES have been demonstrated to be safe in elective patients with relatively simple lesions, whereas no data are available on the safety of PES implantation in patients with acute and subacute MI, conditions usually associated with angiographic evidence of extensive coronary thrombosis which carries a high risk[13-16] of acute reocclusion of the target vessel.

Although previous preclinical reports[17,18] have shown that at higher doses paclitaxel reduces re-endothelialization in coronary vessels with a tendency toward incomplete healing thus potentially increasing the incidence of thrombosis, our results indicate that PES implantation is as safe as bare metal stents even in patients with acute and subacute MI. In fact, in our population both during hospitalization and at short-term follow-up, no adverse event related to acute or subacute thrombosis (death, early post-acute MI angina, reinfarction, target vessel revascularization) was documented. It is interesting to note that the mean value of the corrected TIMI frame count measured in the culprit vessel of our patients immediately after the procedure was comparable to that previously described (< 23) as corresponding to a "fast TIMI flow 3" and related to an adequate tissue perfusion and to a lower incidence of in-hospital complications[19].

The reocclusion rates as well as the incidence of post-procedural complications in our investigation are comparable to those reported after primary angioplasty and standard stent placement[20]. Moreover, in patients submitted to PES implantation, the mean length of hospitalization was not longer than in those in whom standard stents were implanted in our catheterization laboratory[21].

It is worth noting that PES implantation in subacute MI was not associated with any acute or subacute in-stent thrombosis. Despite the small number of patients included, this finding is quite interesting, especially taking into account the presence of extensive coronary thrombosis in this clinical setting (TIMI thrombus grade ≥ 2 in the majority of our patients).

The small number of patients included could constitute one limitation of the present investigation. However, this study population is representative of the "real world" of interventional cardiology, taking into account that we also included patients with subacute MI in whom PES implantation proved to be as safe as in patients with acute MI. Besides, the fact that there were no events in our population can be attributed both to the small group of patients included in the study and to the short term of follow-up. That is why a long-term angiographic, ongoing, follow-up has been scheduled 9 months after PCI. Nevertheless, the aim of the present investigation was to assess the early outcome of PES implantation, and our results, though obtained in a small population, are quite encouraging.

In conclusion, PES implantation for patients with acute and subacute MI is safe, with early outcomes at least comparable to those of conventional standard stents. In our population, no adverse events were observed during the first months following hospital discharge. However, the short length of follow-up does not allow us to draw any definite conclusions regarding the incidence of in-stent restenosis in the long term following PES implantation. Therefore, the validation of PES as a useful strategy in the treatment of MI is warranted and further studies including larger cohorts of patients are needed to confirm our findings and to evaluate the impact of PES implantation on clinical events for patients with MI.

References

1. Stone GW, Grines CL, Cox DA, et al, for the CADILLAC Investigators. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002; 346: 957-66.

2. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1999; 341: 1949-56.
3. Morice MC, Serruys PW, Sousa JE, et al, for the RAVEL Study Group. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002; 346: 1773-80.
4. Moses JW, Leon MB, Popma JJ, et al, for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349: 1315-23.
5. Lemos PA, Lee C, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes. Insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol 2003; 41: 2093-9.
6. Saia F, Lemos PA, Lee C, et al. Sirolimus-eluting stent implantation in ST-elevation acute myocardial infarction. A clinical and angiographic study. Circulation 2003; 108: 1927-9.
7. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six and twelve-month results from a randomized, double-blind trial on a slow release paclitaxel-eluting stent for de novo coronary lesions. Circulation 2003; 107: 38-42.
8. Colombo A, Drzewiecki J, Banning A, et al, for the TAXUS II Study Group. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. Circulation 2003; 108: 788-94.
9. Tanabe K, Serruys PW, Grube E, et al. TAXUS III Trial: in-stent restenosis treated with stent-based delivery of paclitaxel incorporated in a slow-release polymer formulation. Circulation 2003; 107: 559-64.
10. Stone GW, Ellis SG, Cox DA, et al, for the TAXUS IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med 2004; 350: 221-31.
11. Gibson CM, Cannon CP, Daley WL, et al, for the TIMI 4 Study Group. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996; 93: 879-88.
12. Gibson CM, de Lemos JA, Murphy SA, et al, for the TIMI Study Group. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction. A TIMI 14 substudy. Circulation 2001; 103: 2250-4.
13. Violaris AG, Melkert R, Herman JP, Serruys PW. Role of angiographically identifiable thrombus on long-term luminal renarrowing after coronary angioplasty. A quantitative angiographic analysis. Circulation 1996; 93: 889-97.
14. Agrawal SK, Ho DS, Liu MW, et al. Predictors of thrombotic complications after placement of a flexible coil stent. Am J Cardiol 1994; 73: 1216-9.
15. Ellis SG, Roubin GS, King SB, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation 1988; 77: 372-9.
16. Detre KM, Holmes DR, Holubkov R, et al. Incidence and consequences of periprocedural occlusion. The 1985-1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation 1991; 82: 739-50.
17. Farb A, Heller PF, Shroff S, et al. Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. Circulation 2001; 104: 473-9.
18. Drachman DE, Edelman ER, Seifert P, et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. J Am Coll Cardiol 2000; 36: 2325-32.
19. Hamada S, Nishiue T, Nakamura S, et al. TIMI frame count immediately after primary coronary angioplasty as a predictor of functional recovery in patients with TIMI 3 reperfused acute myocardial infarction. J Am Coll Cardiol 2001; 38: 666-71.
20. Wilson SH, Bell MR, Rihal CS, Bailey KR, Holmes DR, Berger PB. Infarct artery reocclusion after primary angioplasty, stent placement, and thrombolytic therapy for acute myocardial infarction. Am Heart J 2001; 141: 704-10.
21. Margheri M, Meucci F, Falai M, et al. Transferring patients for direct coronary angioplasty: a retrospective analysis of 135 unselected patients with acute myocardial infarction. Ital Heart J 2001; 2: 921-6.