Eur J Gen Med 2004; 1(4): 53-64

ORIGINAL ARTICLE

CLINICAL AND ANGIOGRAPHIC RESULTS OF PERCUTANEOUS EXCIMER LASER VERSUS BALLOON ANGIOPLASTY FOR CORONARY INTRA-STENT RESTENOSIS

Aytaç Vural[1], Igor V. Pershukov[2], Talantbek A. Batyraliev[1], Zarema A. Niyazova-Karben[1], Alexandru Karaus[3] Oleg Calenici[3], Larisa N. Petrakova[4],Marina K. Peresypko[4], Dmitry V. Preobrazhenskii[4], Boris A. Sidorenko[4]

INTERNATIONAL CLINICAL AND INVASIVE CARDIOLOGY RESEARCH GROUP
Sani Konukoglu Medical Center, Gaziantep, Turkey[1], Regional Clinical Hospital, Voronezh, Russia[2], Cardiology Institute, Kishineu, Moldova[3], Presidential Medical Center, Central Clinical Hospital, Moscow, Russia[4]

Treatment of in-stent restenosis (ISR) with conventional PTCA causes significant recurrent neointimal tissue growth in 30-85% of the cases. Therefore, laser ablation of intra-stent neointimal hyperplasia prior to balloon dilatation can be an attractive alternative. However, the long-term outcomes of such treatment have not been studied thoroughly enough. This prospective case-control study evaluated angiographic and clinical outcomes of PTCA alone and a combination of excimer laser coronary angioplasty (ELCA) and adjunct PTCA in 125 patients with ISR. ELCA was performed prior to balloon dilatation in 67 patients, PTCA alone was performed in 58 patients. Basic demographic and clinical data were comparable in both groups. Lesions included in ELCA group were longer (17.1±9.9 mm versus 13.6±9.1 mm; p=0.034), more complex (36.5% type-C stenoses versus 14.3%; p=0.006) and more frequently had reduced distal blood flow (TIMI < 3: 18.9% versus 4.8%; p=0.025) compared to lesions in PTCA group. Immediate angiographic results of PTCA and ELCA+PTCA appeared to be comparable. PTCA alone was successful in 57 patients (98.3%), ELCA+PTCA - in 66 patients (98.5%). The rates of hospital complications were comparable (3.0% in ELCA group versus 8.6% in PTCA group). The 1 year-follow-up showed that the rates of MACE were comparable in the two groups (37.3% in ELCA group versus 46.6% in PTCA group). The rates of TVR within 1 year after the intervention were also similar in ELCA and PTCA groups (32.8% versus 34.5%). The data mean that ELCA in patients with complex ISR is efficient and safe. Despite a higher complexity of lesions in ELCA group, no increase in the rate of complications was registered.

Key words: Excimer laser coronary angioplasty, in-stent restenosis, percutaneous transluminal coronary angioplasty

INTRODUCTION

The randomized clinical research has demonstrated a greater efficacy of coronary stenting (CS) in comparison with percutaneous transluminal coronary angioplasty (PTCA) for the treatment of native coronary lesions in patients with coronary artery disease (CAD) (1,2). Stents have been widely used for efficient treatment of coronary lesions of various complexity. At present CS is performed in as many as 50-80% patients at a large number of catheterization laboratories (3). Optimized antithrombotic therapy has significantly decreased acute and subacute complications (4).

However, restenosis is registered with 10-40% of patients within six months after CS (5). In USA alone the number of patients with in-stent restenosis (ISR) is over 150000 a year (6).

It is known that restenosis after PTCA is determined by early elastic recoil, subsequent contraction of the dilated vessel, thrombosis at the site of dilatation, major proliferation with migration to intimal tissue and overproduction of extracellular matrix (7-9). The last two processes are mainly responsible for neointimal tissue growth (7,10). Intravascular ultrasound (IVUS) studies have shown that elastic recoil and subsequent contraction of the dilated vessel are virtually absent after CS (9,11,12). In-stent restenosis results totally from neointimal hyperplasia within the axial

Correspondence: *Igor V. Pershukov, MD, PhD, International Clinical & Invasive Cardiology Research Group, Bolshaya Manezhnaya Street, 14–7, Voronezh, 394000, Russia*
E-mail: pershukov@yahoo.co.uk

stent length and at the margins of the stented segment (12-14).

A large number of strategies have been employed to treat ISR (15,16). The recurrence rate of ISR after conventional PTCA has been reported to be 30-85% depending on the reference vessel diameter and ISR length (17-19). In patients with ISR with a high risk of restenosis efficacy of directional (20-22), high-speed rotational (23-26) and extractional atherectomy (27-29) preceding PTCA was evaluated. The methods allowed to eliminate neointimal hyperplasia before balloon dilatation of ISR and, therefore, contributed to a higher PTCA efficacy and lower residual stenosis. Similarly to atherectomy, excimer laser coronary angioplasty (ELCA) was performed prior to PTCA in patients with a high risk of restenosis (30-31). Its immediate effect has proved to be favorable, but the long-term outcomes of ELCA in the treatment of ISR have not been thoroughly studied, at least in Europe and Asia (32).

This prospective case-control study compared immediate angiographic results and also hospital and long-term clinical outcomes of ELCA + adjunct PTCA with PTCA alone for the treatment of in-stent restenosis. Eight participating clinical centers obtained results on patients after invasive treatment of ISR from tertiary observers united by the research protocol of the International Invasive Cardiology Research Group.

MATERIAL AND METHODS

Patients selection and exclusion criteria

One hundred twenty-five patients hospitalized between 1997 and 2002 with in-stent restenosis were studied. All restenoses and occlusions within a stent were available for both laser ablation and conventional PTCA. Patients with acute myocardial infarction and with cardiogenic shock were excluded from the study. Patients whose follow-up monitoring was impossible were also excluded. Prior written informed consent to every type of invasive treatment was obtained from all patients.

Evaluation of procedural, in-hospital and long-term outcomes

Demographic data were collected from the patients with in-stent restenosis including history of angina, previous myocardial infarctions, number of previous coronary interventions, risks of atherosclerosis and restenosis. Non-invasive examination was performed to grade angina pectoris and estimate significance of the present in-stent restenosis. Diagnostic coronarography determined the number and localization of previously implanted stents, quantitative coronary analysis for the evaluation of ISR was performed.

The intervention of ISR was considered successful if residual stenosis was less than 50% of the vessel diameter and there were no major adverse cardiac events (death, acute occlusion with subsequent myocardial infarction, urgent coronary artery bypass grafting). Subacute occlusion was defined as complete vessel closure outside of the catheterization laboratory within 30 days after the procedure.

Hospital outcome was considered as favorable if after the intervention and up to the hospital discharge there were no major adverse cardiac events (MACE): death, acute myocardial infarction, subsequent target percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).
All the patients were contacted by telephone after their hospital discharge to identify late adverse clinical events: death, myocardial infarction, target vessel revascularization (TVR) in other clinics. In case of recurrent angina all the patients underwent control angiography with subsequent TVR.

Treatment of in-stent restenosis

ELCA was performed according to the above-described technique (32). Eccentric and concentric 1.4 mm, 1.7 mm and 2.0 mm laser catheters were used. Initially the treatment was performed with the smallest 1.4 mm catheter because of safety concerns. If the result was insufficient and a 1.4 mm laser catheter could pass successfully distal to the lesion, a 1.7 mm eccentric laser catheter was chosen. Multiple passes with the catheter were made through the stenotic segment. If a suboptimal result was achieved with a 1.7 catheter, a 2.0 mm concentric laser catheter was used to maximize restenotic tissue ablation. ELCA was discontinued if it was not possible to increase lumen diameter of the lesion after a larger catheter was used. Laser power was between 35 mJ/mm^2 and 55 mJ/mm^2. Mean power was 46.2±4.9 mJ/mm^2. Saline flush was performed during ELCA to prevent or reduce laser-induced photoacoustic damage of the vessel (33).

Adjunctive conventional PTCA (19) was performed after the laser intervention to achieve 1:1 balloon-to-artery ratio. PTCA without prior laser extraction in the restenotic

Table I. Basic demographic and clinical data.

	ELCA n:67	PTCA n:58	p
Age years	61±12	63±12	ns
Women (%)	19 (28.4%)	15 (25.9)	ns
Unstable angina (%)	35 (60.3%)	48 (71.6%)	ns
Prior myocardial infarction (%)	31 (46.3%)	33 (56.9%)	ns
Prior coronary artery bypass grafting (%)	33 (49.3%)	32 (55.1%)	ns
Diabetes mellitus (%)	23 (34.3%)	17 (29.3%)	ns
Family history of CAD (%)	37 (55.2%)	39 (67.2%)	ns
Hypercholesterolemia (%)	50 (74.6%)	37 (63.8%)	ns
Current smokers (%)	31 (46.3%)	34 (60.3%)	ns
Congestive heart failure (%)	16 (23.9%)	13 (22.4%)	ns

CAD; coronary artery disease, ELCA; excimer laser coronary angioplasty, PTCA; percutaneous transluminal coronary angioplasty, ns; non significant

segment was also performed conventionally (19), and the optimal balloon-to-artery ratio of 1:1 was achieved.

Drug support

After the intervention all the patients were treated with heparin intravenously for 24-48 hours, clopidogrel 300 mg in the first 24 hours and 75 mg/day for subsequent 8 weeks. The treatment with aspirin 325 mg/day was routinely continued in all patients.

X-ray analysis

The morphology of the in-stent restenosis was evaluated in accordance with the above-determined standard criteria (34). The length of in-stent restenosis was determined by the axial lumen diameter loss over 50% of the reference vessel diameter. Lesion complexity was evaluated on the scale approved by the American College of Cardiology (ACC) and the American Heart Association (AHA) (35). Complications related to ELCA or PTCA were also recorded.

Preintervention and postintervention angiography of the lesion was performed in two projections. Projections with the least shortening of the lesion were selected. Patients were treated with nitroglycerin intracoronary (200 mcg) before the procedure if no contraindications were reported. A guiding catheter filled with contrast media was used as the calibration device. Mean reference vessel diameter (RVD), minimum lumen diameter (MLD) and diameter stenosis (DS) were calculated using QuantCor QCA 4.0 (Siemens, Germany) QCA-Plus (Sunders Systems, USA) software. To distinguish between intra-stent stenosis and lesions continuing beyond the stent margins into contiguous segments, the first point was chosen at 3-5 mm proximal to the stent and the last point – at 3-5 mm distal to the stent.

Statistical analysis

Continious data are presented as mean ± standard deviation. Qualitative evaluation was performed using chi-square criterion or Fisher's exact test. Proportions were compared using z-test with Yates' correction or Fisher's exact test. Comparison of the end points results was performed using Student's t-test. Stepwise logistic regression model with inclusion of variables was applied to define variables related to MACE developed within 12 months after the intervention. Survival function was estimated using Kaplan and Meier method. Group differences in the proportion of patients without MACE were revealed with Cox F-test. Significant level was considered as $p<0.05$. A software package "Statistica 6.0" (StatSoft Inc) was used for the analysis.

RESULTS

Patients demographic characteristics and clinical data; A total of 125 patients were enrolled in the study. The mean age of the patients was 62±11 years. ELCA was performed in 67 patients (ELCA group); it was immediately followed by PTCA. In 58 patients PTCA alone without prior laser ablation of the restenosis was performed (PTCA group). No significant differences in basic demographic and clinical data between the groups were revealed. Risks of atherosclerosis and restenosis were reported with most patients in both groups. Demographic and clinical data are presented in Table 1.

Angiographic analysis; Initial X-ray coronary angiography was performed in

Table 2. Basic initial angiographic data.

	ELCA n:67	PTCA n:58	p
Lesions with restenosis	74	63	
Number of original stents	1.6±0.6	1.5±0.7	ns
Primary restenosis	65 (87.8%)	60 (95.2%)	ns
Secondary restenosis	8 (10.8%)	2 (3.2%)	ns
Repeat restenosis	1 (1.4%)	1 (1.6%)	ns
Days from stent placement	144±87	162±73	ns
Coronary segment			
LAD	30 (40.5%)	21 (33.3%)	ns
Left circumflex artery	8 (10.8%)	9 (14.3%)	ns
Right coronary artery	19 (25.7%)	13 (20.7%)	ns
Saphenous vein graft	17 (23.0%)	20 (31.7%)	ns
Lesion location			
Ostial	19 (25.7%)	18 (28.6%)	ns
Proximal	25 (33.8%)	16 (25.4%)	ns
Middle	23 (31.7%)	20 (31.7%)	ns
Distal	6 (8.1%)	7 (11.1%)	ns
Anastomosis	1 (1.3%)	2 (3.2%)	ns
Length (mm)	17.1±9.9	13.6±9.1	0.034
Length > 10 mm	57 (77.0%)	30 (47.6%)	0.001
Length > 20 mm	26 (35.1%)	10 (15.9%)	0.019
Eccentric	17 (23.0%)	12 (19.0%)	ns
Bend > 45 degrees	1 (1.4%)	2 (3.2%)	ns
Pre TIMI flow < 3	14 (18.9%)	3 (4.8%)	0.025
Total occlusion	4 (5.4%)	1 (1.6%)	ns
ACC/AHA complexity			
Type A	8 (10.8%)	13 (20.6%)	ns
Type B_1	24 (32.4%)	30 (47.6%)	ns
Type B_2	15 (20.3%)	11 (17.5%)	ns
Type C	27 (36.5%)	9 (14.3%)	0.006

ELCA; excimer laser coronary angioplasty, PTCA; percutaneous transluminal coronary angioplasty, LAD; left anterior descending coronary artery, TIMI; thrombolysis in myocardial infarction, ACC; American College of Cardiology, AHA; American Heart Association, ns; non significant

125 patients with ISR. Hemodynamically significant in-stent restenosis (over 50%) was revealed in 137 segments.

Restenosis-to-patient ratio was 1.1. ELCA+PTCA was performed in 67 patients to treat 74 lesions out of the total 137 lesions. 63 lesions in 58 patients were treated with PTCA alone. Basic initial angiographic data are presented in Table 2. Over fifty percent of the lesions in ELCA group and nearly fifty percent of the lesions in PTCA group were located in branches of the left coronary artery. Lesions in saphenous vein grafts made a considerable proportion in both groups: 23% in PTCA group and 32% in ELCA group. Proliferative restenoses were registered significantly more often in ELCA group. Lesions complexity was higher in ELCA group.

The number of stents was comparable in both groups. Recurrent restenosis was more frequent in ELCA group. In all the patients the stents were multicellular matrix steel constructions. Recurrence period for in-stent restenosis was slightly shorter in ELCA group.

Procedural results; During ELCA the maximum catheter diameter was 1.4 mm in 8 patients (10.8%), 1.7 mm in 26 patients (35.1%) and 2.0 mm in 40 patients (54.1%). 776±513 pulses were delivered during 3.6±2.1 laser catheter passes.

Thrombosis developed in 4 treated segments (5.4%) during ELCA, but remained only in 2 segments (2.7%) after PTCA. In PTCA group thrombosis was registered in one segment (1.6%, differences between the groups not significant). Blood flow reduced below TIMI 3 in 5 segments (6.8%) after ELCA, but after PTCA antegrade blood flow TIMI 3 was registered in all the segments.

Table 3. Quantitative angiographic results.

	ELCA	PTCA	p
RVD, mm			
Initial	2.75±0.63	2.89±0.68	ns
Post ELCA	2.75±0.61		
Final	2.81±0.59	2.93±0.61	ns
MLD, mm			
Initial	0.85±0.41	1.14±0.51	0.001
Post ELCA	1.42±0.49		
Final stent	2.29±0.60	2.25±0.63	ns
Final segment	2.21±0.58	2.19±0.65	ns
% DS			
Initial	69.1±14.1	60.6±14.8	0.001
Post ELCA	48.4±16.9		
Final stent	18.5±13.3	23.2±15.1	ns
Final segment	21.4±12.7	25.3±14.1	ns
Balloon:artery ratio	1.09±0.11	1.03±0.13	0.004

ELCA; excimer laser coronary angioplasty, PTCA; percutaneous transluminal coronary angioplasty, RVD; reference vessel diameter, MLD; minimum lumen diameter, DS; diameter stenosis, ns; non significant

There was no reduction in blood flow after the procedure in PTCA group. Laser treatment caused dissection in 14 segments (18.9%). According to the classification of the National Heart, Lung and Blood Institute, type A and B dissections immediately after ELCA were registered in 8 segments (4+4), type C and D dissections – in 6 segments (3+3). No type E or F dissections were registered. Dissections after PTCA were registered in 17 segments in ELCA group (23.0%). Type A was registered in 3 segments (4.1%), type B – in 7 segments (9.5%), type C – in 5 segments (6.8%), and type D – in 2 segments (2.7%). Type E or F dissections were not registered. In PTCA group dissections appeared after balloon dilatation in 10 segments (15.2%, differences between the groups not significant). Type B dissection was registered in 4 segments (6.3%), type C – in 5 segments (7.9%) and type D – in 1 segment (1.6%).

Generally, the outcome of ELCA was not optimal in 5 cases (6.8%). In 2 cases a lesion could not be passed to its full length, in 3 other cases the reasons were different. However, successful results were obtained in 4 out of 5 non-optimal ELCA cases after PTCA was performed. Thus, in ELCA group the treatment of in-stent restenosis appeared to be ineffective in 1 case (1.5%). In PTCA group the treatment of in-stent restenosis was not successful in 1 patient (1.7%) due to the massive vessel thrombosis. ELCA+PTCA treatment was significantly more time-consuming: it was 67.2±41.9 minutes versus 49.3±35.6 minutes in PTCA group (p:0.012).

Quantitative coronary analysis of the laser and balloon interventions (Table 3) showed that the reference vessel diameter was comparable in both groups. However, in ELCA group there were more patients with the smaller minimum lumen diameter (0.85 mm versus 1.14 mm in PTCA group, $p<0.001$). Mean residual stenosis after ELCA was less than 50%: 48.4%±16.9%. There were no significant differences between the groups in final MLD and DS. Significant differences were registered in the maximum balloon diameter-to-reference vessel diameter ratio: in ELCA group it was significantly larger (1.09 versus 1.03 in PTCA group, p:0.004).

Hospital results; Immediate effect was achieved in 66 out of 67 patients in ELCA group (98.5 %), and in 57 out of 58 patients in PTCA group (98.3 %, difference not significant). In 2 patients (1 patient in each group) endovascular treatment of ISR was complicated by a massive thrombosis of coronary arteries. Urgent coronary artery bypass grafting was needed. Both operations were successful; the thrombotic occlusion did not result in myocardial infarction with Q-wave. During the hospital stay target PTCA at the site of in-stent restenosis was performed in 4 patients in PTCA group and in 1 patient in ELCA group due to recurrent angina (the tendency for more frequent target interventions in PTCA group was not significant). 2 out of 4 patients in PTCA group suffered acute coronary syndrome. Successful intravenous thrombolysis with streptokinase was performed which prevented development of acute myocardial infarction. 1 patient in ELCA group and 1 patient in PTCA group

Table 4. Procedural and in-hospital outcomes

	ELCA	PTCA	p
n	67	58	
Procedural success	66 (98.5%)	57 (98.3%)	ns
Urgent CABG	1 (1.5%)	1 (1.7%)	ns
Recurrent angina	1 (1.5%)	4 (6.9%)	ns
Repeat PCI	1 (1.5%)	4 (6.9%)	ns
All in-hospital complications	2 (3.0%)	5 (8.6%)	ns
Clinical success	65 (97.0%)	53 (91.4%)	ns

ELCA; excimer laser coronary angioplasty, PTCA; percutaneous transluminal coronary angioplasty, CABG; coronary artery bypass grafting, ns; non significant

underwent target PCI with tirofiban - blocker of glycoprotein IIb/IIIa platelet receptors. None of the interventions caused cardiac tamponade. All the patients were alive at the time of hospital discharge. Complications and hospital outcomes are presented in Table 4.

Cardiac complications and bleedings after the intervention were minimal in both groups. No retroperitoneal hematoma, ischemic limbs or major bleedings with hematocrit reduction were registered. There were no instances of gastrointestinal bleeding or cerebrovascular hemorrhages. One arteriovenous fistula in ELCA group (1.5%) and one pseudoaneurysm in each group (1.5% in ELCA group and 1.7% in PTCA group) were not typical for the groups, did not result in clinical complications and did not make any significant intergroup differences.

Long-term clinical outcomes; Clinical events during the 12 month-follow-up are presented in Table V. No significant intergroup differences were revealed concerning cardiac death rate, development of Q-wave myocardial infarction, recurrent angina CCS class. II-IV, need for target PCI or CABG. The average follow-up period and complications occurrence period after the procedure were 222 ± 97 days in ELCA group and 200 ± 103 days in PTCA group (differences not significant). Totally, MACE took place in 25 patients from ELCA group (37.3%) and in 27 patients in PTCA group (46.6%, differences not significant). TVR (coronary angioplasty or coronary artery bypass grafting) of the restenotic vessel was needed in 32.8 % in ELCA group and in 34.5 % in PTCA group (differences not significant).

Evaluation of cumulative proportions of patients without MACE was performed with Kaplan and Meier method (Figure1). When compared using the criterion for censored data (Cox F-test:1.50), a tendency for less frequent complications in ELCA group proved to be non-significant (p:0.07).

Stepwise logistical regression model with inclusion of variables was applied to reveal demographic, clinical, angiographic and procedural factors significantly related to the recurrent restenosis after the treatment of ISR. The analysis has shown that the period of time from the first stenting until ISR (odds ratio OR:8.81, range 1.21÷42, p: 0.03), diabetes mellitus (OR=3.72, range 1.43÷9.94, p:0.017), the length of the in-stent restenosis (OR=2.85, range 1.19÷6.85, p:0.012) and female gender (OR=1.65, range 1.11÷2.98, p:0.04) are significant predictors of the recurrent restenosis and of the need for

Table 5. Late clinical outcome.

	ELCA	PTCA	p
n	67	58	
MACE	25 (37.3%)	27 (46.6%)	ns
Time to follow-up, days	222±97	200±103	ns
Death	1 (1.5%)	2 (3.4%)	ns
Q-wave MI	2 (3.0%)	1 (1.7%)	ns
Recurrent angina	20 (29.9%)	19 (32.8%)	ns
All TVR	22 (32.8%)	20 (34.5%)	ns
Target lesion CABG	7 (10.4%)	8 (13.8%)	ns
Target lesion PCI	15 (22.4%)	12 (20.7%)	ns

ELCA; excimer laser coronary angioplasty, PTCA; percutaneous transluminal coronary angioplasty, MACE; major adverse cardiac events (death, MI, TVR, recurrent angina), MI; myocardial infarction, TVR; target vessel revascularization, CABG; coronary artery bypass grafting, PCI; percutaneous coronary intervention, ns; non significant

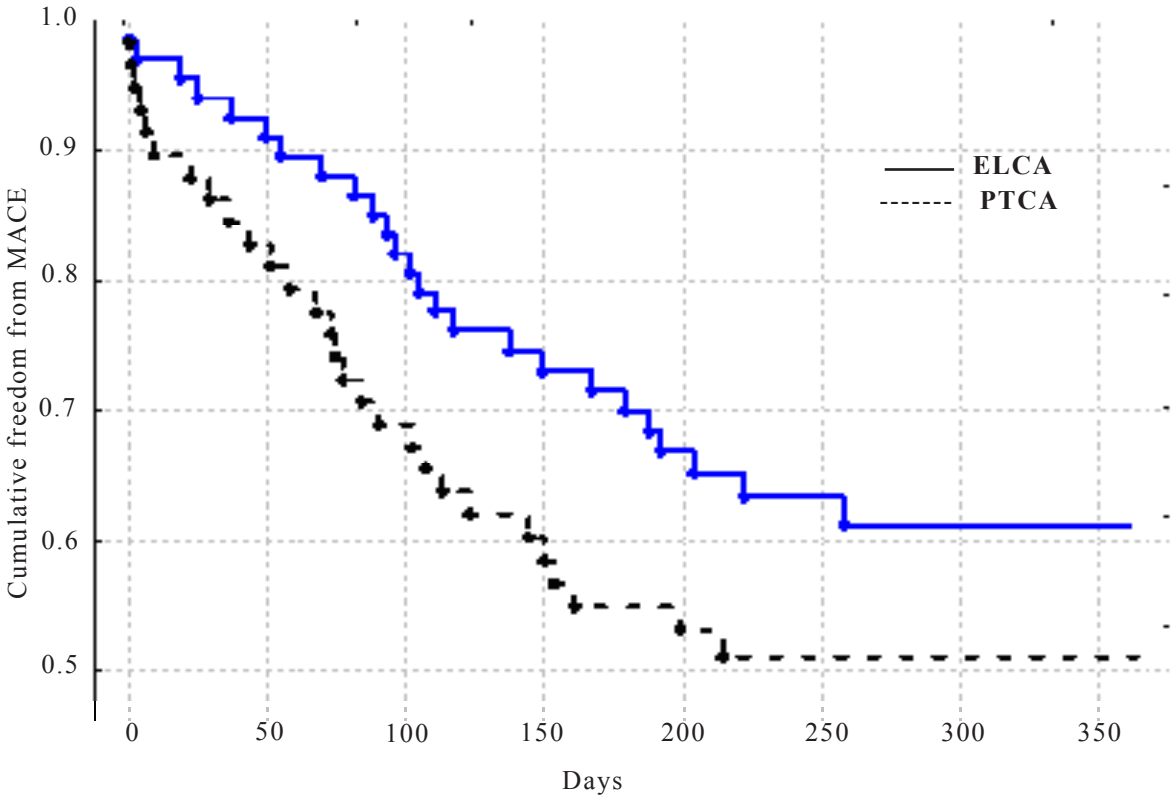

Figure 1. Cumulative freedom from MACE at follow-up (Kaplan-Meier method).

target revascularizations. At the same time, a bigger reference vessel diameter has proved to be a significant predictor (OR=0.59, range 0.28÷0.87, p:0.01) of lower recurrence rate for ISR and related complications.

DISCUSSION

There is an acute demand for the best strategy to treat in-stent restenosis, because the number of stent implantations and ISR after the intervention are increasing every year, and the recurrence rate for dilated restenotic vessels is varying from 30% to 85% (17-19). This study demonstrates safety and efficacy of ELCA for the treatment of ISR. This revascularization technique has a high potential for the treatment of complex lesions. Despite sufficient length of the ISR (17.1±9.9 mm) and lesions complexity (type B2 or C lesions were registered in 56.8% cases), the number of revascularizations within the 12 month-follow-up after ELCA was 32.8%. However, the proportion of target revascularizations was comparable in both groups and the study has not demonstrated significant clinical advantage of ELCA+adjunct PTCA for the treatment of ISR compared to PTCA alone. A larger-scale comparison of the methods may be required to reveal advantages of laser treatment of ISR. However, a study conducted in the USA which compared efficacy of ELCA and PTCA used for the treatment of 157 lesions in 146 patients did not reveal significant differences between the methods, although it mentioned a trend for more favorable outcomes after ELCA (37).

Treatment of in-stent restenosis; Serial IVUS studies have shown that the base for restenosis after conventional PTCA is chronic which may contribute as much as 75% to the lumen loss (10-11). On the contrary, lumen loss after the stenting results primarily form neointimal tissue growth within the axial length of the stent (11-14). It is in very rare instances that ISR is caused by underdilation of the stent or by its radial compression (6,12-14,38). Marginal restenosis is, therefore, more often caused by the combination of mechanical stenosis and tissue growth (12,13,37). Previous research using angiographic and IVUS data showed that diffuse ISR (over 10 mm) was significantly related to the stent length, reference lumen diameter and final diameter at the site of implantation (35,39).

The revascularization strategy was

determined by three basic mechanisms of the treatment of ISR. Neointimal redistribution, plaque ablation or elimination and stent expansion are required (14,31). Longitudinal and cross lumen plaque can be redistributed inside a stent towards its margins and through the stent cells into the media and adventitia only during balloon expansion. Quantitative evaluation of IVUS studies showed that dilatation if ISR with the balloon alone significantly increased minimal lumen cross-sectional area (CSA) from 2.3±1.3 mm^2 to 6.1±2.2 mm^2 ($p<0.0001$); in-stent lumen CSA increased from 7.2±2.4 mm^2 to 8.7±2.6 mm^2 and in-stent neointimal hyperplasia CSA reduced from 4.9±2.2 mm^2 to 2.7±2.0 mm^2 ($p<0.0001$) (40).

In 1990s a number of single- and multicenter trials were conducted to evaluate efficacy of endovascular treatment of in-stent restenosis, which developed after first coronary stent models were implanted (17-19,40,41).

These studies demonstrated, in particular, safety and efficacy of balloon dilatation of 75 restenoses in Gianturco-Roubin wire stents (19). Immediate success of the dilatation of ISR was 97%, MACE were registered in 1.3% cases. ISR reduced by 57% from 77%±12% to 20%±11%. Opportunities for endovascular treatment of restenosis within the first matrix Palmaz-Schatz stent were considered even more favorable. Immediate success of balloon dilatation reached to 100%, no MACE including subacute occlusion outside of the catheterization laboratory were registered (18). In a later multicenter study immediate success of PTCA in treatment of ISR was 98.4%, but in 6.4% cases early target PTCA was required during the same in-hospital stay. The reasons were major dissections and rapid prolapse of the crushed plaque into the stent lumen. Target PTCA was successful in all the patients. In the present study immediate success of PTCA without laser ablation of ISR was 98.3%; hospital outcome without complications was 91.4%. As in the previous study, TVR was needed in 8.6% patients due to early recurrent angina.

On the contrary, long-term outcomes of balloon dilatation of ISR were less favorable. The rate of recurrent angina requiring TVR was reported to be from 14% to 81% depending on the length of the initial ISR (17,18,40). One report indicated development of recurrent ISR in 37% cases after PTCA (17). In case of diffuse ISR (over 10 mm), the recurrence rate was 85% compared to 12% in case of local ISR and 19% in case of marginal restenosis ($p<0.0001$). Another study also registered a tendency for a higher recurrence rate of ISR and its TVR after PTCA if ISR was longer than 10 mm (41% recurrence rate in case of diffuse ISR and 19% recurrence rate in case of local ISR, p:0.08) (40). A randomized comparison of PTCA and ELCA in the treatment of ISR has demonstrated that the recurrence rate for local and noncomplicated ISR and for related events was 32.3% after PTCA (37), whereas this nonrandomized study after PTCA alone has registered a recurrence rate of 34.5% for in-stent restenosis and its target revascularizations performed within the first 6 moths after PTCA. The high recurrence rate for ISR emphasized the urgent need for developing alternative strategies to treat in-stent restenosis.

Alternative strategies for the treatment of in-stent restenosis; Elimination of in-stent neointimal hyperplasia prior to PTCA in patients with a high risk of recurrence of ISR can result in considerable reduction of the substrate for subsequent neointimal tissue growth. For this, extractional (27-29,43), directional (20-22) and high-speed rotational (23-26) atherectomy was applied. It appeared that atherectomy with adjunct PTCA results in a greater final lumen of the restenotic segment. The largest number of clinical data refer to the use of high-speed rotational atherectomy. Several research groups have reported good immediate outcomes and low hospital complications after high-speed rotational atherectomy with adjunct PTCA (23-26). An interesting comparison was performed for high-speed rotational atherectomy and ELCA. IVUS control after extraction and laser ablation showed that high-speed rotational atherectomy eliminated more neointimal tissue (31), but it was difficult to directly compare efficacy of the two extractional methods. The main restriction on the use of high-speed rotational atherectomy is the fixed bur diameter of 2.5 mm. Since a bur diameter must be approximately 80% of a vessel diameter, the use of high-speed rotational atherectomy in vessels of a non-matching diameter is related to a greater risk of complications. Besides, a frequent effect of high-speed rotational atherectomy used in patients with ISR is an elevation of MB fraction of creatine phosphokinase (23).

Directional atherectomy has more advantages in the treatment of ISR, because it allows target elimination of large masses of neointimal hyperplasia (22,42). An

atherectom has a bigger cutting diameter compared to a rotating bur. In a series of trials the final lumen was larger after directional atherectomy than after PTCA (2.7±0.4 mm versus 2.2±0.5 mm, p<0.0005), and late events were less frequent after directional atherectomy than after PTCA (10.5% versus 39%, p:0.03) (42). The main restrictions on the use of directional atherectomy are the necessity to use guiding catheters of a large diameter 10F (3.3 mm), a possibility of partial elimination of the stent and complexity of working with lesions longer than 15 mm and also in vessels less than 3 mm (20,21).

ELCA in the treatment of in-stent restenosis; Tissue ablation by excimer laser energy can be an efficient way to eliminate plaques in patients with ISR (30,32,37,44). In-stent lumen gain is achieved by the combination of tissue ablation, tissue redistribution and stent expansion (30,32). A single-center study used IVUS to evaluate volume and distribution of ISR after PTCA and after ELCA (32). It appeared that immediate outcomes were more favorable in ELCA group than in PTCA group. Another study of 23 patients with 37 restenotic segments in stents evaluated immediate and short-term effect of ELCA. ELCA achieved 100% effect in 15 cases of ISR after Palmaz-Schatz stents implantation and in 22 cases of ISR after AVE-Microstent stents implantation (30). To achieve the effect, average 634±396 pulses were delivered during 29±16 seconds. The maximum laser diameter was 1.4 mm in 2 cases, 1.7 mm in 14 cases and 2.0 mm in 7 cases. ELCA resulted in significant reduction of the stenosis from 75±16% to 44±13% (p<0.01), and adjunct PTCA contributed to its further reduction to 19±14% (p<0.01). Procedural outcomes were successful in all cases, no dissections or perforations were visualized.

Despite the more aggressive character of atherectomy and laser ablation, the final lumen diameter of the restenotic stent was smaller than the primary lumen achieved during the initial stenting (45,46). In 159 patients with in-stent restenosis, PTCA, ELCA or high-speed rotational atherectomy resulted in the increase of the lumen cross-sectional area (CSA) from 2.1±1.4 mm^2 to 6.2±1.7 mm^2 according to IVUS, reduced neointimal hyperplasia with tissue ablation and plaque extrusion from 5.5±2.4 mm^2 to 2.9±1.6 mm^2, and also further expanded the stent from 7.5±2.3 mm^2 to 9.1±2.4 mm^2. However, the final lumen CSA measured 1.3±1.9 mm^2, which was less than before the intervention (46). When residual stenosis developed due to dissection or the plaque prolapse into the lumen, additional stenting was required (47). 18% of significant residual stenosis in stented lesions after ELCA appeared to be non-significantly less than 22% of significant residual stenosis after PTCA, which is considerably greater than 10% of residual stenosis after the initial restenting of ISR. Recently, Koster et al. received non-optimal results after ELCA treatment of 141 segments in 96 patients (48). After 6 months the rate of restenosis (over 50% of a vessel diameter) was 54%, target endovascular interventions were performed in 31% of cases; in 18% of patients coronary artery bypass grafting was needed.

On the other hand, a multicenter LARS (Laser Angioplasty for Restenotic Stents) trial conducted in the USA by Giri et al. revealed a higher potential of ELCA for the treatment of complex in-stent restenoses in 93 patients (37). Success was achieved in 98.9% of cases, and major adverse events were registered in 1.1%. One vessel perforation was not directly related to ELCA, because it was diagnosed after adjunct PTCA. In other cases no dissections restricting blood flow were registered. The need for target PTCA was less after ELCA (1.1%) than after PTCA (6.4%). Long-term outcomes up to 1 year were also more favorable after ELCA. Major cardiac complications occurred in 39.1% of cases after ELCA and in 45.2% after PTCA within the period. Target revascularizations were performed in 30% of patients after ELCA, and in 32.3% of patients after PTCA.

The results of this study conducted in Europe are largely similar to the ones obtained by the American trial LARS. As there was no randomization, more complex in-stent lesions were included in ELCA group. However, the immediate outcomes of ELCA and PTCA were comparable. ELCA+adjunct PTCA was successful in 98.5% of patients, PTCA alone – in 98.3%. Hospital complications were more frequent after PTCA (8.6%) than after ELCA+PTCA (3.0%), but this trend was not significant. In-hospital monitoring showed that adverse cardiac events occurred in 37.3% of patients after ELCA and in 46.6% after PTCA, target revascularizations were required in 32.8% and 34.5% respectively. Survival analysis did not demonstrate significance of the tendency for less frequent complications in ELCA group. However, during the entire follow-up

period the curve of cumulative proportion of the patients without complications in ELCA group was above the curve for PTCA group.

As a result, since the study was planned in a nonrandomized design and a bigger number of patients with more severe ISR were included in ELCA group, it is not possible to draw a conclusion about advantages of excimer laser treatment of in-stent restenosis. However, the high rate of successful interventions (98.5%), the low rate of in-hospital complications (3.0%) and acceptable rate of MACE within 365 days after the procedure (37.3%) allow to recommend ELCA with adjunctive conventional PTCA for the treatment of in-stent lesions of various complexity.

REFERENCES

1- 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: Benestent Study Group. N Engl J Med 1994;331:489–95
2- 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: Stent Restenosis Study Investigators. N Engl J Med 1994;331:496–501
3- Peterson ED, Lansky AJ, Muhlbaier LH, et al. Evolving trends in angioplasty device selection: a National Cardiovascular Network (NCN) database report. J Am Coll Cardiol 1997;29:495A
4- Batyraliev TA, Pershukov IV. Review of clinical studies of ischemic heart disease and its invasive treatment. Kardiologiia, 2002;42(5):68–70
5- Belenkov YN, Batyraliev TA, Pershukov IV. Invasive Cardiology – Focus on Restenosis. Part I. Kardiologiia 2002;42(8):50–6
6- Belenkov YuN, Batyraliev TA, Pershukov IV. Invasive Cardiology–Focus on Restenosis. Part II. Kardiologiia 2002;42(11):68–72
7- Schwartz RS. Animal models of human coronary restenosis. In Topol EJ, ed. Textbook of Interventional Cardiology. 2nd ed. Philadelphia, PA: W.B. Saunders, 1994:365–81
8- Moreno PR, Palacios IF, Leon MN, Rhodes J, Fuster V, Fallon JT. Histopathologic comparison of human coronary in-stent and postballoon angioplasty restenotic tissue. Am J Cardiol 1999;84:462–6
9- Mach F. Toward new therapeutic strategies against neointimal formation in restenosis. Atheroscler Thromb Vasc Biol 2000;20:1699–700
10- Mintz GS, Popma JJ, Pichard AD et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 1996;94: 35–43
11- Mudra H, Regar E, Klauss V et al. Serial follow-up after optimized ultrasound guided deployment of Palmaz-Schatz stents. Circulation 1997;95:363–70
12- Hoffmann R, Mintz GS, Dussaillant GR et al. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. Circulation 1996;94: 1247–54
13- Hoffmann R, Mintz GS, Popma JJ et al. Chronic arterial responses to stent implantation: a serial intravascular ultrasound analysis of Palmaz-Schatz stents in native coronary arteries. J Am Coll Cardiol 1996;28:1134–9
14- Gordon PC, Gibson CM, Cohen DJ et al. Mechanism of restenosis and redilation within coronary stents-quantitative angiographic assessment. J Am Coll Cardiol 1993;21:1166–74
15- Mehran R, Dangas G, Abizaid A et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–8
16- Goldberg SL, Loussararian A, De Gregorio J, Di Mario C, Albiero R, Colombo A. Predictors of diffuse and aggressive intrastent restenosis. J Am Coll Cardiol 2001;37:1019–25
17- Yokoi H, Kimura T, Nakagawa Y et al. Long-term clinical and quantitative angiographic follow-up after the Palmaz-Schatz stent restenosis. J Am Coll Cardiol 1996;27:224A
18- Baim DS, Levine MJ, Leon MB, et al. Management of restenosis within the Palmaz-Schatz coronary stent: the U.S. multicenter experience – the U.S. Palmaz-Schatz Stent Investigators. Am J Cardiol 1993;71:364–6
19- Macander PJ, Roubin GS, Agrawal SK, et al. Balloon angioplasty for treatment of in-stent restenosis: feasibility, safety, and efficacy. Cathet Cardiovasc Diagn 1994;32:125–31
20- Bowerman RE, Pinkerton CA, Kirk B, Waller BF. Disruption of a coronary stent during atherectomy for restenosis. Cathet Cardiovasc Diagn 1991;24:248–51

21- Meyer T, Schmidt T, Buchwald A, Wiegand V. Stent wire cutting during coronary directional atherectomy. Clin Cardiol 1993;16:450–2
22- Strauss BH, Umans VA, van Suylen RJ et al. Directional atherectomy for treatment of restenosis within coronary stents: clinical, angiographic and histologic results. J Am Coll Cardiol 1992;20:1465–73
23- Bottner RK, Hardigan KR. High-speed rotational ablation for in-stent restenosis. Cathet Cardiovasc Diagn 1997;40:144–9
24- Klues HG, Reffelmann T, von Dahl J, Hanrath DP. High-speed rotational coronary atherectomy for the treatment of restenosis in coronary stents. J Am Coll Cardiol 1997;29:313A
25- Schiele F, Meneveau N, Vuillemenot A et al. Rotational atherectomy followed by balloon angioplasty for treatment of restenosis in coronary stents. J Am Coll Cardiol 1997;29:498A
26- Buchbinder M, Goldberg SL, Fortuna R et al. Rotational atherectomy for intra-stent restenosis: initial experience. Circulation 1996;94:I621
27- Hara K, Ikari Y, Tamura T, Yamaguchi T. Transluminal extraction atherectomy for restenosis following Palmaz-Schatz stent implantation. Am J Cardiol 1997;79: 801–2
28- Goods CM, Jain SP, Liu MW et al. Intravascular ultrasound-guided transluminal extraction atherectomy for restenosis after Gianturco-Roubin coronary stent implantation. Cathet Cardiovasc Diagn 1996;37:317–9
29- Ikari Y, Yamaguchi T, Tamura T et al. Transluminal extraction atherectomy and adjunctive balloon angioplasty for restenosis after Palmaz-Schatz coronary stent implantation. Cathet Cardiovasc Diagn 1993;30:127–30
30- Koster RP, Koschyk DH, Kahler J et al. Laser angioplasty on in-stent restenosis. Circulation 1996;94(Suppl):I621
31- Mehran R, Mintz GS, Popma JJ et al. Mechanisms of lumen enlargement during atheroablation of in-stent restenosis: a volumetric ultrasound analysis. J Am Coll Cardiol 1997;29:497A
32- Mehran R, Mintz GS, Satler LF et al. Treatment of in-stent restenosis with excimer laser coronary angioplasty: mechanisms and results compared with PTCA alone. Circulation 1997;96:2183–9
33- Deckelbaum LI, Natarajan MK, Bittle JA et al. Effect of intracoronary saline infusion on dissection during excimer laser coronary angioplasty: a randomized trial. J Am Coll Cardiol 1995;26:1264–9
34- Popma JJ, Bashore TM. Qualitative and quantitative angiographic. In: Topol, editor. Textbook of Interventional cardiology. Philadelphia: W.B. Saunders; 1993. p 1052–68
35- Ellis SG, Roubin GS, King SB III et al. Importance of stenosis morphology in the estimation of restenosis risk after elective percutaneous transluminal coronary angioplasty. Am J Cardiol 1989;63:30–4
36- van der Zwet PM, Reiber JH. A new approach for the quantification of complex lesion morphology: the gradient field transform – basic principles and validation results. J Am Coll Cardiol 1994;24:216–24
37- Giri S, Ito S, Lansky AJ et al. Clinical and angiographic outcome in the Laser Angioplasty for Restenotic Stents multicenter registry. Cathet Cardiovasc Diagn 2001;52:24–34
38- Painter JA, Mintz GS, Wong SC et al. Serial intravascular ultrasound studies fail to show evidence of chronic Palmaz-Schatz stent recoil. J Am Cardiol 1995;75: 398–400
39- Mehran R, Mintz GS, Pichard AD et al. Morphologic and procedural predictors of diffuse in-stent restenosis. J Am Coll Cardiol 1997;29:76A
40- Mehran R, Mintz GS, Popma JJ et al. Mechanism and results of balloon angioplasty for the treatment of in-stent restenosis. Am J Cardiol 1996;78:618–22
41- Sharma SK, Rajawat Y, Kakarala V et al. Angiographic pattern of in-stent restenosis after Palmaz-Schatz stent restenosis. J Am Coll Cardiol 1997;29:313A
42- Pathan A, Butte A, Harrell M et al. Directional coronary atherectomy for the treatment of Palmaz-Schatz stent restenosis. J Am Coll Cardiol 1997;29: 68A
43- Chow WH, Chan TF. Pullback atherectomy for the treatment of intrastent restenosis. Cathet Cardiovasc Diagn 1997;40:94–5
44- Topaz O, Vetrovec GW. The stenotic stent: mechanisms and revascularization options. Cathet Cardiovasc Diagn 1996;37:293–9
45- Schiele F, Meneveau N, Vuillemenot A, et al. Intracoronary ultrasound assessment of balloon angioplasty in intrastent restenosis. J Am Coll Cardiol 1997;29:

240A.
46- Mehran R, Mintz GS, Popma JJ et al. Treatment of in-stent restenosis: a intravascular ultrasound study of results in 159 stented lesions. J Am Coll Cardiol 1997;29:77A
47- Moris C, Alfonso F, Lambert JL et al. Stenting for coronary dissection after balloon dilation of in-stent restenosis: stenting a previously stented site. Am Heart J 1996;131:834–6
48- Koster R, Kahler J, Terres W et al. Six-month clinical and angiographic outcome after successful excimer laser angioplasty for in-stent restenosis. J Am Coll Cardiol 2000;36:69–74