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Clinical events following excimer laser angioplasty or balloon angioplasty for complex coronary lesions: subanalysis of a randomised trial

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Abstract

Objectives—To compare clinical outcome in patients with complex coronary lesions treated with either excimer laser coronary angioplasty (ELCA) or balloon angioplasty.

Patients and design—308 patients with stable angina and a coronary lesion of more than 10 mm in length were randomised to ELCA (151 patients, 158 lesions) or balloon angioplasty (157 patients, 167 lesions). The primary clinical end points were death, myocardial infarction, coronary bypass surgery, or repeated coronary angioplasty of the randomised segment during six months of follow up. Subanalysis was performed to identify a subgroup of patients with a beneficial clinical outcome following ELCA or balloon angioplasty.

Setting—Two university hospitals and one general hospital.

Results—There were no deaths. Myocardial infarction, coronary bypass surgery, and repeated angioplasty occurred in 4.6, 10.6, and 21.2%, respectively, of patients treated with ELCA compared with 5.7, 10.8, and 18.5%, respectively, of those treated with balloon angioplasty. ELCA did not yield a favourable clinical outcome in subgroups of patients with long (more than 20 mm) coronary lesions, calcified lesions, small diseased vessels (≤ 2.5 mm reference diameter), or total coronary occlusions. There was a worse clinical outcome in patients with tandem lesions treated with ELCA compared with balloon angioplasty (9/18 v 3/26 lesions; $p = 0.01$); while a trend towards an unfavourable clinical outcome was found in patients with vessels with a reference diameter of more than 2.5 mm (23/66 v 13/63 lesions, $p = 0.07$) and left circumflex coronary lesions (12/41 v 6/42 lesions, $p = 0.08$).

Conclusions—The findings indicate a worse clinical outcome in patients with lesions of more than 10 mm treated with ELCA compared with balloon angioplasty who have tandem coronary lesions and in those with vessels with a reference diameter of more than 2.5 mm and left circumflex coronary lesions.

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Keywords: excimer laser angioplasty; laser assisted balloon angioplasty; balloon angioplasty; randomised trial; interventional cardiology

Excimer laser coronary angioplasty (ELCA) was introduced as an alternative technique for the treatment of obstructive coronary lesions because of the unique features of the laser system facilitating precise tissue ablation with minimal adjacent injury.^{1–3} These characteristics were considered optimal for application in patients with diffuse coronary artery disease. ELCA registries indicated favourable clinical and angiographic outcomes in patients with complex coronary lesions, such as long coronary lesions (more than 10 mm), calcified lesions, small diffusely diseased vessels (≤ 2.5 mm), ostial lesions, venous graft lesions, or total coronary occlusions, compared with those in patients treated by balloon angioplasty.^{4–7} These promising results led to a randomised trial in 1991 comparing the effects ELCA and balloon angioplasty in patients with stable angina and longer coronary lesions (more than 10 mm in length).^{8,9} Similar initial and long term clinical and angiographic outcomes were reported for patients treated with ELCA (followed by balloon angioplasty in 98% of the procedures) or balloon angioplasty.

The aim of the present study was to identify a subgroup of patients with a beneficial clinical outcome following either excimer laser assisted balloon angioplasty or balloon angioplasty.

Patients and methods

Patients were randomised between September 1991 and November 1993 in the Amsterdam-Rotterdam trial (AMRO) comparing ELCA with balloon angioplasty in the treatment of patients with stable angina and long (more than 10 mm) native coronary lesions including total or functional occlusion (thrombolysis in myocardial infarction (TIMI) flow grade 0 or I).¹⁰ The randomisation process, inclusion and exclusion criteria, and procedural protocols of the laser and balloon angioplasty procedures have been described.⁹ The excimer laser systems (wavelength 308 nm) used were Dymor 200+ (Advanced Interventional Systems (AIS), Irvine, California, USA), with a pulse duration of 210 ns and a repetition rate of 20 Hz, delivered by multifibre over wire laser catheters with a diameter of 1.3, 1.6, or 2.0 mm, at a fluence of 45–65 mJ/mm², and the CVX-300 system (Spectranetics, Colorado

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Springs, Colorado, USA), which emits a pulse duration of 135 ns at a repetition rate of 25 Hz, delivered by 1.4, 1.7, or 2.0 mm laser catheters, with a similar fluence. The 1.3 mm laser catheter (AIS) was used after its introduction in 1992. The 1.3/1.4 mm laser catheter was used for vessels with a diameter of between ≥ 1.8 mm and < 2.3 mm; the 1.6/1.7 mm laser catheter for vessels with a diameter of between ≥ 2.3 mm and < 3.0 mm; and the 2.0 mm laser catheter for vessels with a diameter of ≥ 3.0 mm. The 1.3/1.4 mm laser catheter was used as the initial laser catheter in total and functional occlusions. Adjunctive balloon angioplasty was performed at the operator's discretion. Conventional balloon angioplasty was performed according to the standard clinical practice of the operator.

QUANTITATIVE ANGIOGRAPHY

Coronary angiography was performed in multiple projections, identically repeated before and after the procedure and at six months' follow up. Angiography was carried out according to previously published guidelines for automated analysis at the core laboratory using the cardiovascular angiographic analysis system.¹¹

CLINICAL AND ANGIOGRAPHIC FOLLOW UP

Patients were seen after one and six months for interview, physical examination, and an electrocardiogram. Follow up angiography was performed after six months. Repeat intervention was carried out if recurrent symptoms of angina occurred or there was objective evidence of myocardial ischaemia and a percentage diameter stenosis of more than 50% on visual assessment of the randomised lesion, or both.

END POINTS

Primary clinical end points were any of the following events during six months, (\pm one month) follow up: cardiac death, myocardial infarction (based on the presence of at least two of the following criteria: typical chest pain and/or a rise in the serum concentration of myocardial creatine kinase of more than twice the normal upper limit and/or new pathological Q wave formation on the electrocardiogram), coronary bypass surgery, or a repeat angi-

oplasty because of recurrent symptoms of angina and/or objective evidence of myocardial ischaemia by positive exercise testing, all presumably related to the randomised segment. Coronary bypass surgery included emergency or elective bypass surgery. All clinical events were reviewed by the critical event committee, which was unaware of the treatment assignment.

VARIABLES IN THE SUBGROUP ANALYSIS

Baseline clinical and angiographic variables were related to the occurrence of clinical events during six months' follow up in both treatment groups.

The following clinical variables were analysed: sex, age, diabetes, hypertension, hypercholesterolaemia, smoking status, previous myocardial infarction, previous balloon angioplasty, previous coronary bypass grafting, exertional angina graded according to the Canadian Cardiovascular Society classification,¹² non-exertional angina, and the extent of coronary artery disease. The following angiographic variables were analysed: location of the randomised lesion, type of lesion defined as ulcerated/irregular contour of the lesion; calcified lesion defined as fixed radiographic densities within the randomised lesion, ranging from mild (barely visible) to severe (spine density); eccentric lesion defined as a highly asymmetric appearance of the randomised stenosis in any angiographic projection; tandem lesion defined as sequential narrowing in the same randomised coronary segment; grade of perfusion of the randomised segment before intervention (TIMI flow grade 0, I, II, or III); type of lesion according to the modified American College of Cardiology/American Heart Association task force criteria,¹³ and estimated length of lesion.

The following quantitative variables were analysed: interpolated reference diameter, length of lesion, and percentage diameter stenosis before angioplasty related to the randomised lesion.

STATISTICAL ANALYSIS

Continuous variables (age, length of lesion, reference diameter, percentage diameter stenosis) were divided in dichotomous variables by cut off points based on clinical relevance reported in previous investigations. Age was divided between those who were 70 years or older and those who were less than 70; reference diameter between vessels of 2.5 mm or less and those of more than 2.5 mm; and length of lesion between less than 20 mm or 20 mm or more. Lesion severity was analysed in three arbitrary subgroups of increasing percentage diameter stenosis as 70%, 70–90%, and 90%. Chi square analysis and Fisher's exact test for two by two tables were used to compare dichotomous variables. Subgroup analysis was performed to evaluate the relation between baseline clinical and angiographic variables and the occurrence of clinical events in both groups. Clinical events occurring in relation to baseline clinical and angiographic variables were compared with the calculated relative risk and 95% confidence intervals. All

Table 1 Clinical events occurring during six months' follow up in the 308 patients randomised to excimer laser angioplasty (ELCA) or balloon angioplasty (BA)

Patients	ELCA (%) (n=151)	BA (%) (n=157)	Relative risk (95% CI)	p value
Primary clinical end point	50 (33.1)	47 (29.9)	1.11 (0.80 to 1.93)	0.55
Death	0	0	—	
Myocardial infarction	7 (4.6)	9 (5.7)	0.81 (0.31 to 2.12)	0.67
Q wave				
Periprocedural	2 (1.3)	2 (1.3)	1.04 (0.15 to 7.29)	0.97
Follow up	2 (1.3)	1 (0.6)	2.08 (0.19 to 22.70)	0.54
Non-Q wave				
Periprocedural	3 (2.0)	3 (1.9)	1.04 (0.21 to 5.07)	0.96
Follow up	0	3 (1.9)	0.15 (0.01 to 2.85)	0.09
CABG	16 (10.6)	17 (10.8)	0.98 (0.51 to 1.87)	0.95
Periprocedural	7 (4.5)	3 (1.9)	2.43 (0.64 to 9.21)	0.18
Follow up	9 (6.0)	14 (8.9)	0.67 (0.30 to 1.50)	0.32
Repeat angioplasty	32 (21.2)	29 (18.5)	1.15 (0.73 to 1.80)	0.55
Periprocedural	2 (1.3)	3 (1.9)	0.69 (0.12 to 4.09)	0.68
Follow up	30 (19.9)	26 (16.6)	1.20 (0.75 to 1.93)	0.45

Primary clinical end point: death, myocardial infarction, coronary artery bypass grafting (CABG), or repeat angioplasty.

Table 2 Analysis of the relation between important baseline clinical and angiographic variables and the occurrence of clinical events in the 308 patients randomised to excimer laser angioplasty (ELCA) or balloon angioplasty (BA)

Patients	ELCA (%) (n=151)	BA (%) (n=157)	Relative risk (95% CI)	p value
Primary clinical end point	50/151 (33.1%)	47/158 (29.9%)	1.11 (0.80 to 1.54)	0.55
<i>Clinical variables</i>				
Male	37/115 (32.1%)	32/114 (28.1%)	1.15 (0.77 to 1.70)	0.50
Female	13/36 (36.1%)	15/43 (34.9%)	1.04 (0.57 to 1.88)	0.91
≥70 years	11/25 (44.0%)	11/28 (39.3%)	1.12 (0.59 to 2.12)	0.73
<70 years	39/126 (30.9%)	36/129 (27.9%)	1.11 (0.76 to 1.62)	0.59
Diabetes	6/15 (40.0%)	7/20 (35.0%)	1.14 (0.48 to 2.70)	0.76
Hypertension	21/57 (36.8%)	17/50 (34.0%)	1.08 (0.65 to 1.81)	0.76
Hypercholesterolemia	23/58 (39.7%)	18/59 (30.6%)	1.30 (0.79 to 2.14)	0.30
Smoking status				
Never	15/41 (36.6%)	15/50 (30.0%)	1.22 (0.68 to 2.19)	0.51
Previous	25/74 (33.8%)	23/68 (33.8%)	1.00 (0.63 to 1.58)	1.00
Current	7/33 (21.2%)	7/34 (20.6%)	1.03 (0.41 to 2.62)	0.95
History of MI	22/70 (31.4%)	24/68 (35.3%)	0.89 (0.56 to 1.43)	0.63
History of BA	3/16 (18.8%)	4/25 (16.0%)	1.17 (0.30 to 4.56)	1.00
History of CABG	3/10 (30.0%)	2/13 (15.4%)	1.95 (0.40 to 9.54)	0.62
Exertional angina				
CCS class I+II	16/56 (28.6%)	15/58 (25.9%)	1.10 (0.61 to 2.02)	0.75
CCS class III+IV	34/95 (35.8%)	32/99 (32.3%)	1.11 (0.75 to 1.64)	0.61
Extent of coronary artery disease				
Monovessel	27/83 (32.5%)	22/79 (27.8%)	1.17 (0.73 to 1.87)	0.52
Multivessel	23/68 (33.8%)	25/78 (32.1%)	1.06 (0.66 to 1.68)	0.82
Lesions	n=158	n=167		
Primary clinical end point	52/158 (32.9%)	51/167 (30.6%)	1.08 (0.78 to 1.48)	0.65
<i>Angiographic variables</i>				
Location of lesion				
LAD	25/61 (40.9%)	26/64 (40.6%)	1.01 (0.66 to 1.54)	0.97
RCA	15/56 (26.8%)	19/61 (31.2%)	0.86 (0.49 to 1.52)	0.60
LCx	12/41 (29.3%)	6/42 (14.3%)	2.05 (0.85 to 4.94)	0.08
Type of lesion				
B2	30/83 (36.1%)	23/71 (32.4%)	1.12 (0.72 to 1.73)	0.63
C	22/74 (29.7%)	27/94 (28.7%)	1.04 (0.64 to 1.66)	0.89
Ulcerated	17/53 (32.1%)	15/55 (27.3%)	1.18 (0.66 to 2.11)	0.58
Calcified	9/33 (27.3%)	10/39 (25.6%)	1.06 (0.49 to 2.30)	0.88
Eccentric	30/100 (30.0%)	33/104 (31.7%)	0.95 (0.63 to 1.43)	0.79
Tandem	9/18 (50.0%)	3/26 (11.5%)	4.33 (1.36 to 13.83)	0.01
Estimated lesion length				
10 to 20 mm	39/122 (31.9%)	35/109 (32.1%)	1.00 (0.68 to 1.45)	0.98
>20 mm	12/33 (36.4%)	11/44 (25.0%)	1.45 (0.74 to 2.88)	0.28
Grade of perfusion				
0 + I	15/49 (30.6%)	12/54 (22.2%)	1.38 (0.72 to 2.65)	0.33
II + III	37/109 (33.9%)	39/113 (34.5%)	0.98 (0.68 to 1.42)	0.93
<i>Quantitative variables</i>				
Reference diameter (mm)				
≤2.5	26/76 (34.2%)	35/88 (39.7%)	0.86 (0.58 to 1.29)	0.46
>2.5	23/66 (34.8%)	13/63 (20.6%)	1.69 (0.94 to 3.03)	0.07
Length (mm)				
<20	25/79 (31.6%)	24/73 (32.9%)	0.96 (0.61 to 1.53)	0.87
≥20	12/35 (34.3%)	14/50 (28.0%)	1.22 (0.64 to 2.33)	0.54
Diameter stenosis (%)				
≤70	30/98 (30.6)	35/106 (33.0%)	0.93 (0.62 to 1.39)	0.71
70 to 90	7/18 (38.9%)	4/18 (22.2%)	1.75 (0.62 to 4.95)	0.28
>90	15/42 (35.7%)	12/43 (27.9%)	1.28 (0.68 to 2.40)	0.44

Primary clinical end point: death, myocardial infarction (MI), coronary artery bypass grafting (CABG), repeat angioplasty; CCS, angina classification according to the Canadian Cardiovascular Society classification system;¹² LAD, left anterior descending coronary artery; RCA, right coronary artery; LCx, left circumflex coronary artery; Type of lesion, according to the modified ACC/AHA Task Force criteria;¹³ Grade of perfusion, according to the TIMI study group.¹⁰

statistical analyses were performed using the statistical analysis system program. A p value of less than 0.05 was considered significant.

Results

Baseline clinical and angiographic characteristics were similar. A total of 308 patients (325 lesions) were randomised to either laser angioplasty (151 patients, 158 lesions) or balloon angioplasty (157 patients, 167 lesions). Laser success, defined as a reduction of more than 20% in percentage diameter stenosis by visual assessment, was achieved in 107 (68%) of 158 lesions treated by laser angioplasty. The angiographic success rate, defined as a less than 50% diameter stenosis at the end of the procedure by visual assessment, was achieved in 126

(80%) of the 158 lesions treated with laser angioplasty and in 132 (79%) of the 167 lesions treated with balloon angioplasty. Laser angioplasty was followed by additional balloon angioplasty in 98% of procedures to obtain an angiographic optimal result. Table 1 lists periprocedural major clinical events and those that occurred during six months' follow up. There was no mortality. The incidence of myocardial infarction, coronary bypass grafting, and repeat angioplasty was similar periprocedurally and at six months in both groups. Clinical follow up was completed in 98% of patients in each group.

SUBGROUP ANALYSIS

Table 2 compares clinical outcome in patients treated with laser angioplasty or balloon angioplasty in relation to baseline clinical and angiographic variables during six months' follow up. The occurrence of a major clinical event in association with different clinical variables was similar in both groups.

The randomised lesion being located in the left anterior descending coronary artery was associated with a higher incidence of clinical events independent of treatment allocation, compared with the randomised lesion being located in the right coronary artery or left circumflex.

At baseline, patients with lesions with a reference diameter of more than 2.5 mm and who were treated with laser angioplasty experienced more clinical events than patients treated with balloon angioplasty (p = 0.07). Location of the randomised lesion in the left circumflex artery was associated with a higher incidence of clinical events in the laser angioplasty group than in the balloon angioplasty group (p = 0.08). Furthermore, treatment of a tandem lesion with laser angioplasty was associated with a significant adverse clinical outcome compared with that in patients treated with balloon angioplasty (p = 0.01).

Twenty per cent of patients with diseased vessels with a reference diameter of more than 2.5 mm assigned to laser angioplasty, had a tandem lesion and 21% of patients had a left circumflex coronary lesion. Moreover, 7% of patients with a left circumflex coronary lesion had a tandem lesion.

Discussion

ECLA: RANDOMISED VERSUS NON-RANDOMISED

Non-randomised ELCA registries show high initial success rates and low complication rates for complex coronary lesions that are considered less suitable for balloon angioplasty.^{4-7 14 15}

In the present study, a subanalysis of the randomised trial comparing excimer laser angioplasty with balloon angioplasty for longer (more than 10 mm) coronary lesions,⁹ excimer laser angioplasty did not have a favourable clinical outcome in patients with long (more than 20 mm) coronary lesions, small diameter vessels (≤2.5 mm), calcified lesions, or total coronary occlusions.

Our study differs from the reports of ELCA registries because of the randomised design of the trial. First, the trial is a prospective collec-

tion of clinical and angiographic data monitored in a meticulous fashion with almost complete follow up. Second, quantitative coronary analysis was performed by an independent core laboratory, while the registries reported data from core laboratories with incomplete follow up or used data based on visual or quantitative analysis performed at the participating institutions.^{4-6 14} Third, the incidence of procedural myocardial infarction in the present study was determined routinely by measuring the concentration of serum creatine kinase after each procedure. In contrast, myocardial infarction in the ELCA registries was detected by either electrocardiographic criteria or enzymatic measurements, which were not performed on a routine basis.^{4-6 14 15} This may explain the observed differences. Our results are similar to those in studies in which enzymatic evaluation was determined routinely as part of the procedure.^{16 17}

ECLA: RANDOMISED CLINICAL TRIALS

A recently reported randomised trial compared the clinical and angiographic results of rotational atherectomy, ELCA, and balloon angioplasty, namely the excimer laser, rotational atherectomy, and balloon angioplasty comparison (ERBAC) trial.¹⁸ Although a higher proportion of patients with type C lesions or long coronary lesions (more than 20 mm) were included in our trial, both trials show a large demand for additional balloon angioplasty (93% in the ERBAC trial *v* 98% in the AMRO trial). The results agree with those of our trial showing no advantage of ELCA compared with that of balloon angioplasty in terms of procedural outcome and the number of in-hospital events (12% in the ERBAC trial *v* 9% in the AMRO trial). The primary goals of the ERBAC trial were procedural outcome and in-hospital events and, as a consequence, follow up angiography was not performed in all patients (75% in the ERBAC trial *v* 93% in the AMRO trial). Nevertheless, the incidence of revascularisation procedures was higher in patients treated with ELCA (46% in the ERBAC trial *v* 26% in the AMRO trial), while there was a trend towards an unfavourable angiographic outcome in these patients. Data from both trials indicates that ELCA, compared with balloon angioplasty, does not result in improved clinical and angiographic outcome.

SUBGROUP ANALYSIS OF ECLA VERSUS BALLOON ANGIOPLASTY FOR COMPLEX CORONARY LESIONS

The present study included patients with longer (more than 10 mm) coronary lesions on the basis that excimer laser angioplasty would have a beneficial effect on their outcome. A subanalysis of the ELCA registries indicated a favourable outcome in lesions of more than 20 mm in length, calcified lesions, total coronary occlusions, and small diseased coronary vessels.^{4-7 14 15} This reported benefit could not be confirmed in our study.

A worse clinical outcome after treatment with excimer laser angioplasty was seen in patients with tandem lesions and there was a

trend towards an unfavourable clinical outcome in those with vessels with a reference diameter of more than 2.5 mm or left circumflex coronary lesions. An additional analysis showed minimal overlap between the patient groups with respect to these three variables, indicating that they were independent factors with an unfavourable clinical outcome following excimer laser angioplasty. An explanation for our findings is speculative. Most clinical events occurred during follow up indicating that the incidence of clinical events is related to long term effects following excimer laser angioplasty. After excimer laser application, fast expanding and imploding vapour bubbles induce damage in the vascular wall and mechanical dilatation, which may result in accelerated neointima hyperplasia,^{19 20} or unfavourable vascular remodelling of the coronary segment.²¹

The observation that excimer laser angioplasty results in an unfavourable clinical outcome in vessels with a reference diameter of more than 2.5 mm suggests that other techniques, such as coronary stent implantation or coronary atherectomy,²² are more appropriate for treatment of larger sized vessels. The observed unfavourable clinical outcome in left circumflex coronary lesions requires further investigation as it refers to a substantial number of patients studied. Furthermore, the incidence of clinical events is particularly low in the balloon angioplasty group. The explanation for the worse clinical outcome in tandem lesions is speculative, as it refers to only a few patients. Finally, the higher incidence of clinical events irrespective of treatment after intervention in the left anterior descending coronary artery is in accord with results in other reports.²³

STUDY LIMITATIONS

This study concerns the results of a randomised trial comparing ELCA versus balloon angioplasty, although ELCA was followed by balloon angioplasty in 98% of the procedures. The frequent application of balloon angioplasty following ELCA relates to the recommended size of the laser catheter in comparison with the diameter of the reference segment. Consequently, the results of this study involves a comparison between laser assisted balloon angioplasty and balloon angioplasty alone and does not yield information on the outcome after ELCA alone.

Furthermore, although this study has been performed in the context of a randomised clinical trial, it involves a post-hoc analysis. The total number of patients studied in this trial is relatively small, compared with the numbers reported in some clinical ELCA registry reports,^{15 16} and those recruited in multicentre randomised trials of other devices.²⁴

Recent insights have indicated that the mechanical damage induced by excimer laser angioplasty can be reduced by flushing with saline before laser application.²⁵ This procedure removes blood situated in front of the laser catheter and, consequently, absorption of laser light by blood is reduced. Laser light is not

absorbed by saline,²⁶ and this leads to the decreased production of fast expanding and imploding vapour bubbles and thus to the reduction of vascular wall damage and less dilatation of the coronary segment.²⁰ This trial, however, was conducted between 1991 and 1993 and consequently, no flushing protocol was used. Other applications to optimise the current laser technique, such as use of lower energy fluence during the laser procedure,²⁷ very slow passage with the laser catheter through the lesion, multiplex laser,²⁸ or a modified laser catheter tip,²⁹ are under investigation and may improve the laser technique so that it can be a useful device in the treatment of coronary artery disease.

In conclusion, this randomised study shows that in patients with coronary lesions of more than 10 mm in length treated with excimer laser angioplasty there are no subgroups with a favourable clinical outcome compared with those treated with balloon angioplasty.

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