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Differences in restenosis propensity of devices for transluminal coronary intervention

A quantitative angiographic comparison of balloon angioplasty, directional atherectomy, stent implantation and excimer laser angioplasty

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With the increasing clinical application of new devices for percutaneous coronary revascularization, maximization of the acute angiographic result has become widely recognized as a key factor in maintained clinical and angiographic success. What is unclear, however, is whether the specific mode of action of different devices might exert an additional independent effect on late luminal renarrowing. The purpose of this study was to investigate such a difference in the degree of provocation of luminal renarrowing (or 'restenosis propensity') by different devices, among 3660 patients, who had 4342 lesions successfully treated by balloon angioplasty (n=3797), directional coronary atherectomy (n=200), Palmaz-Schatz stent implantation (n=229) or excimer laser coronary angioplasty (n=116) and who also underwent quantitative angiographic analysis pre- and post-intervention and at 6-month follow-up. To allow valid comparisons between the groups, because of significant differences in coronary vessel size (balloon angioplasty=2·62 ± 0·55 mm, directional coronary atherectomy=3·28 ± 0·62 mm, excimer laser coronary angioplasty=2·51 ± 0·47 mm, Palmaz-Schatz=3·01 ± 0·44 mm; P<0·0001), the comparative measurements of interest selected were the 'relative loss' in luminal diameter (RLoss=loss/vessel size) to denote the restenosis process, and the 'relative lumen at follow-up' (RLfup=minimal luminal diameter at follow up/vessel size) to represent the angiographic outcome.

For consistency, lesion severity pre-intervention was represented by the 'relative lumen pre' (RLpre=minimal luminal diameter pre/vessel size) and the luminal increase at intervention was measured as 'relative gain' (relative gain=gain/vessel size). Differences in restenosis propensity between devices was evaluated by univariate and multivariate analysis. Multivariate models were constructed to determine relative loss and relative lumen at follow-up, taking account of relative lumen pre-intervention, lesion location, relative gain, vessel size and the device used. In addition, model-estimated relative loss and relative lumen at follow-up at given relative lumen pre-intervention relative gain and vessel size, were compared among the four groups. Significant differences were detected among the groups both with respect to these estimates, as well as in the degree of influence of progressively increasing relative gain, on the extent of renarrowing (relative loss) and angiographic outcome (relative lumen at follow-up), particularly at higher levels of luminal increase (relative gain). Specifically, lesions treated by balloon angioplasty or Palmaz-Schatz stent implantation (the predominantly 'dilating' interventions) were associated with more favourable angiographic profiles than directional atherectomy or excimer laser (the mainly 'debulking' interventions). Significant effects of lesion severity and location, as well as the well known influence of luminal increase on both luminal renarrowing and late angiographic outcome were also noted.

These findings indicate that propensity to restenosis after apparently successful intervention is influenced not only by the degree of luminal enlargement achieved at intervention, but by the device used to achieve it. In view of the clinical implications of such findings, further evaluation in larger randomized patient populations is warranted.

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Introduction

Over the last decade, a number of new devices for transluminal coronary revascularization have been introduced, aiming to improve acute and long-term clinical and angiographic results of coronary balloon angioplasty[1,2]. Through a variable combination of

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plaque removal, compression and vessel stretching[3–6], directional coronary atherectomy can achieve significantly greater acute luminal results than conventional balloon angioplasty[7–10], but randomized trials have failed to demonstrate long-term superiority of this apparent mechanical advantage[7,8]. By vaporization of atherosclerotic plaque, excimer laser coronary angioplasty has been associated with improved acute success compared with balloon angioplasty, especially in complex coronary lesions[11–13], but restenosis rates in registry and observational reports have been relatively high[11,13–15] and the results of a recently completed randomized trial demonstrated no difference in clinical or angiographic results between balloon angioplasty and excimer laser angioplasty[16]. Stent implantation, through vessel expansion, opposition of natural elastic recoil[17] and establishment of a smooth and circular coronary lumen[18–20], has the capacity to achieve consistently superior procedural luminal increases compared with balloon angioplasty[18–23]. Although two randomized comparisons of Palmaz-Schatz stent implantation with balloon angioplasty, in native primary coronary stenoses, indicate long-term maintenance of the acute advantage of stent implantation[24,25], it is not yet known whether this is simply due to the greater acute luminal increase, or to additional benefits of specific mechanical or physical properties of the stent itself.

Despite the mechanistic differences between these four devices, uncontrolled observational studies have concluded that the magnitude of the post-procedural lumen alone determines late angiographic outcome, without any detectable independent contribution of the device used to achieve it[10,26]. Conversely, studies in angiographically matched lesions, comparing balloon angioplasty with each of directional atherectomy[9,27], stent implantation[23] and excimer laser[15], as well as unmatched general comparisons[28,29], have reported definite differences in the degree of provocation of luminal renarrowing (or 'restenosis propensity') and late angiographic results between patient groups treated by different devices. Accordingly, the purpose of this study was to attempt to resolve these opposing findings by investigating the possibility of a specific influence of the device used for intervention, using a previously described multiple linear regression approach[30], in a large patient population treated by balloon angioplasty, directional atherectomy, Palmaz-Schatz stent implantation or excimer laser coronary angioplasty.

Population and methodology

The study population was made up of 3660 patients (4342 lesions) treated for native coronary artery disease by balloon angioplasty (n=3797 lesions), directional coronary atherectomy (n=200 lesions), Palmaz-Schatz stent implantation (n=229 lesions) and excimer laser coronary angioplasty (n=116 lesions). Patients treated by balloon angioplasty had been enrolled in four international multicentre placebo-controlled restenosis-prevention trials, the details of which have already been published[31–34]. In each of these trials the pharmacological agent under investigation was found to have no significant effect on either clinical or angiographic outcome by both univariate and multivariate analyses, so, for the purposes of the present study, all the patients were pooled and considered as one group. Patients treated by Palmaz-Schatz Stent implantation had been recruited during a European multicentre randomized comparison with balloon angioplasty, for treatment of native primary coronary artery lesions (associated with stable anginal symptoms) with a reference vessel diameter ≥ 3 mm[24]. Final quantitative angiographic follow-up was 93%. Patients whose therapy was by excimer laser coronary angioplasty were treated at a single institution, using a Xenon Chloride device (Dymer 200+, Advanced Interventional systems, Inc., Irvine, CA, U.S.A.), which emits laser pulses with a wavelength of 308 nm, duration of 210 ns and at a repetition rate of 20 Hz. Over-the-wire laser catheters of 1·3, 1·6 and 2·0 mm, with concentric multifibre arrangement around a central lumen were employed at a fluence of 45–65 mJ . mm^{-2}. The excimer laser procedures were carried out according to conventional practice as previously reported[15]. Adjunctive balloon angioplasty was carried out in 98% of lesions. Quantitative angiographic follow-up among eligible patients was 94%. Patients were treated by directional coronary atherectomy at two specialised institutions (The Thoraxcenter, Rotterdam, Netherlands and St Luc University Hospital Brussels, Belgium, both of which participated in the Coronary Angioplasty Versus Excisional Atherectomy (CAVEAT) trial), using the Simpson atherectomy catheter (Devices for Vascular Intervention, San Diego, CA, U.S.A.). Primary lesions were treated in 80% of cases and 20% of lesions had undergone previous intervention. A 6F device was used in 61% and 7F in 39% of cases, with a mean of $5·9 \pm 2·8$ cuts per lesions. Adjunctive balloon angioplasty was carried out in 16% of lesions. Overall, quantitative angiographic follow-up was 93%. In all component studies, all aspects of intervention were left to the discretion of the individual physician. Successful intervention was universally considered as a post-procedural diameter stenosis of <50% visually assessed by the individual investigator.

QUANTITATIVE CORONARY ANGIOGRAPHIC METHODOLOGY

Coronary angiography was performed in multiple projections pre-intervention and repeated identically immediately after intervention, and at a predetermined 6-month follow-up. The angiograms were recorded to facilitate quantitative analysis by automated edge detection (using the Cardiovascular Angiographic Analysis System (CAAS)), in the angiographic core laboratory, with universal application of specific standardization procedures, as previously described[30,35,36].

QUANTITATIVE ANGIOGRAPHIC MEASUREMENTS OF INTEREST IN THIS STUDY

Due to the wide range of coronary vessel size treated by modern interventional devices, (as confirmed in Table 2 in the results section), quantitative coronary angiographic measurements were normalized for reference vessel size, deriving measurements of 'relative gain' and 'relative loss' in luminal diameter, as previously introduced[9,23,37,38]. The vessel size was represented as the interpolated reference diameter *pre-intervention* as previously described[30,38], since measurement of the reference diameter post-intervention and at follow-up is subject to consequential changes[39,40], especially after stent implantation[17,24]. Accordingly, relative measurements of lumen dimensions pre- and post-intervention and at follow-up were also derived by normalizing minimal luminal diameter for the interpolated reference diameter pre-intervention, producing the measurements of 'relative lumen' pre- and post-intervention and at follow-up, as previously described[41]. These novel parameters thus represent measurements of luminal patency as a fraction of the ideal luminal diameter. *Relative gain*=Gain/Vessel Size; *Relative loss*=Loss/Vessel Size; *Net gain index*=Gain-Loss/Vessel Size; *Relative lumen*=Minimal luminal diameter/Vessel Size. Conventional binary measures of restenosis were also estimated applying a number of commonly used angiographic criteria (Table 2).

STATISTICAL METHODS

Statistical analyses were carried out with the assistance of a commercially available statistical software package (SAS, SAS Institute, Inc.). A lesion-based approach was applied in the analyses, as previously justified[42–44], which assumed that quantitative coronary angiographic measures of restenosis were continuously distributed[22,45]. Analysis of variance was used to compare continuous parameters between the groups. Restenosis rates were compared using a chi-square test. A linear relationship was assumed between relative gain at intervention and relative loss during follow-up, in keeping with the findings of previous studies[6,9,10,14,15,22,23,26–30,42,44] and a recent specific evaluation, which confirmed that a linear relation was the 'best fit' to describe the association between these parameters among patients treated by balloon angioplasty, directional atherectomy or stent implantation[46]. To investigate the influence of the device used on the restenosis process and late angiographic outcome, the relationship between relative luminal gain at intervention and each of relative luminal loss during follow-up (representing the restenosis process) and relative lumen at follow-up (as the late angiographic outcome), was investigated. This was done first in simple linear regression analysis, then the entire patient population was considered as a single group and a previously described multiple linear regression model was constructed, to take account of the respective determining influence of the vessel size, lesion severity pre-intervention (relative lumen pre-intervention), the influence of the physician (relative luminal gain at intervention) and the epicardial lesion location[30].

To investigate whether a difference could exist between the four devices in the degree of relative loss provoked by increasing relative gain (so called 'effect modification'), an 'interaction term' between 'device' and relative gain (denoted in the model as: 'device × gain') was entered as an independent variable. The same procedure was performed for relative lumen pre-intervention, vessel size and lesion location. If an interaction term is found to contribute significantly to the final model, this would imply a significant difference between the devices, with respect to the influence of that particular factor on the late angiographic results. Intergroup comparisons can then be performed to locate the source of the detected difference.

For additional comparative purposes, the multivariate model was interrogated to provide estimates of relative luminal loss and lumen at follow-up for each device group at hypothetical, but clinically relevant, interventional scenarios. Accordingly, we chose to compare estimated outcome between the four devices in this study: firstly for the 'average lesion' undergoing an 'average interventional result'; thus, where mean relative gain (0·30, Table 2) is achieved in a lesion with the mean lumen pre-intervention (0·38, Table 2), in a vessel of mean diameter (2·67 mm, Table 2). Because of the preponderance of lesions treated by balloon angioplasty, the overall mean values for these parameters tend to reflect a typical balloon angioplasty scenario (Table 2), so the second level for comparison of estimated outcome was selected to reflect a typical 'stent/atherectomy intervention'; thus, model-estimated relative loss and lumen at follow-up were compared after achievement of the mean relative gain for the directional coronary atherectomy and Palmaz-Schatz stent groups, in a lesion with the mean relative lumen pre-intervention and vessel size for those groups (i.e. where a relative gain of 0·44 is achieved in a lesion with a relative lumen pre-intervention of 0·37, in a vessel of 3·12 mm). Finally, to evaluate possible differences in late outcome between the devices if an optimal acute result is achieved in a lesion of average severity and in a moderately large vessel, the third level of comparison was chosen to reflect these circumstances (and called 'optimal intervention'). For a lesion of mean severity (0·39, Table 2), in a vessel of 3·2 mm, an optimal acute result would be where the minimal luminal diameter post-intervention was also 3·2 mm, giving a relative lumen post-intervention of 1·0, which in this case, would require a relative gain of 0·61.

Actual statistical comparisons are provided, without systematic automatic correction for 'multiple comparisons', in order to display all potential differences and trends between the groups. To illustrate the findings graphically, three-dimensional regression planes were constructed, as previously described[30].

Results

Baseline demographic features of the patient groups are provided in Table 1. Table 2 displays quantitative

Table 1 Demographic data for the four patient groups

	Balloon angioplasty	Directional atherectomy	Excimer laser	Palmaz-Schatz stent
Patients (n)	3135	190	106	229
Lesions (n)	3796	200	116	229
Male/Female	80%/20%	81%/19%	80%/20%	80%/20%
Age (years)	56 ± 9	58 ± 11	56 ± 9	55 ± 9
Lesion (primary/restenosis)	100%	80%/20%	100%	100%
Vessel				
LAD	43%	67%	36%	65%
RCA	33%	20%	35%	22%
LCX	24%	13%	29%	13%
Total occlusion pre-intervention	6%	0	15%	4%
Diabetes	7%	6%	6%	7%
CCS III or IV angina	52%	73%	72%	64%
Non-exertional angina	46%	40%	52%	48%

LAD=Left anterior descending coronary artery; RCA= right coronary artery; LCX=left circumflex artery; CCS=Canadian Coronary Society.

angiographic measurements pre- and post-intervention and at 6-month follow-up. Vessel size differed widely ($P<0.0001$), justifying the use of relative rather than absolute dimensional parameters. After normalization, significant differences were detected between the groups for all parameters: pre-procedural lesion severity was greatest in the excimer laser coronary angioplasty group, which had the greatest frequency of total occlusion pre-intervention (relative lumen pre-intervention 0·31 or % diameter stenosis 69%). Luminal increase was greatest after Palmaz-Schatz stent implantation (relative gain of 0·48, or 48% increase in lumen) as was post-procedural relative lumen (0·84 or 84% of vessel diameter). Despite having greatest relative loss (0·21, 21% loss in vessel diameter) Palmaz-Schatz stent implantation also retained the greatest relative lumen at follow-up (0·64, or 64% of ideal) and displayed the greatest ultimate net benefit (net gain index 0·28, 28% net increase in vessel diameter).

BINARY RESTENOSIS RATES (TABLE 2)

Differences between the groups in binary restenosis depended on the definition applied (Table 2). Excimer laser coronary angioplasty was associated with the highest frequency of a stenosis $\geq 50\%$ at follow-up at 51%, followed by balloon angioplasty at 36%, directional coronary atherectomy at 29% and Palmaz-Schatz stenting at 16% ($P<0.0001$), although Palmaz-Schatz stent implantation had the greatest frequency of a loss ≥ 0.4 mm during follow-up.

LINEAR REGRESSION ANALYSIS (FIG 1)

Significant differences were detected between the device groups in the relative loss response to increasing relative gain ($P=0.0006$, by analysis of variance; 0·61 in the directional coronary atherectomy group, 0·57 in the excimer laser coronary angioplasty group, 0·37 in the balloon angioplasty group and 0·33 in the Palmaz-Schatz stent group) and in the relative lumen at follow-up response to increasing relative gain ($P=0.003$; −0·22 for excimer laser coronary angioplasty, 0·01 for balloon angioplasty, 0·17 for directional coronary atherectomy and 0·22 for Palmaz-Schatz stenting).

MULTIPLE LINEAR REGRESSION ANALYSIS (TABLE 3, FIG. 2)

Inter-device differences in predicted angiographic results

Each of relative luminal gain, relative lumen pre-intervention and lesion location in the left anterior descending coronary artery were found to be significant independent determinants of both relative loss and relative lumen at follow-up. Having already controlled for the influence of vessel size, by virtue of the use of relative parameters, no significant further independent influence of this parameter on outcome was noted. Significant differences were observed, however, between the devices with respect to the influence of relative gain on each of relative loss and relative lumen at follow-up ($P=0.02$; reflected by the observed differences in the slopes of the three-dimensional regression planes, from right to left in Fig. 2). The principle source of this difference appeared to be between the balloon angioplasty and each of the excimer laser coronary angioplasty ($P<0.01$) and the directional coronary atherectomy ($P=0.04$) groups, whereby, for a given relative luminal gain, 43% would be retained as improved relative lumen at follow-up if balloon angioplasty was used, compared with 23% for directional coronary atherectomy and 12% for excimer laser coronary angioplasty. By Palmaz-Schatz stenting, 41% of relative gain was predicted to be retained as relative lumen at follow-up, which was not found to be statistically different from that predicted for directional coronary atherectomy and excimer laser coronary angioplasty ($P=0.07$ vs excimer laser coronary angioplasty).

Comparison of estimated outcome between devices at the three pre-designated levels of comparison, as already described, revealed the following: for average intervention, significant differences in model-estimated relative

Table 2 Quantitative angiographic measured and derived parameters per device group, given as mean and standard deviation (SD)

	Balloon angioplasty Mean ± SD		DCA Mean ± SD		Laser Mean ± SD		Stent Mean ± SD		All Mean ± SD		ANOVA *P*
Reference diameter pre (mm)	2·62	0·55	3·28	0·62	2·51	0·47	3·01	0·44	2·67	0·57	<0·0001
Reference diameter post (mm)	2·67	0·53	3·34	0·52	2·68	0·49	3·19	0·41	2·73	0·55	<0·0001
Reference diameter f-up (mm)	2·69	0·58	3·32	0·54	2·60	0·60	2·96	0·47	3·09	0·51	<0·0001
MLD pre (mm)	0·99	0·40	1·21	0·38	0·76	0·44	1·08	0·33	1·00	0·40	<0·0001
MLD post (mm)	1·73	0·37	2·41	0·43	1·66	0·39	2·51	0·36	1·80	0·40	<0·0001
MLD f-up (mm)	1·42	0·58	1·83	0·60	1·17	0·71	1·91	0·54	1·46	0·60	<0·0001
Diameter stenosis pre (%)	61·30	14·60	63·20	10·00	68·80	18·30	63·90	10·10	61·80	14·40	<0·0001
Diameter stenosis post (%)	34·70	9·60	27·50	9·80	37·80	10·50	20·90	7·50	33·70	10·10	<0·0001
Diameter stenosis f-up (%)	46·50	19·40	41·00	16·40	55·70	23·60	35·50	14·10	45 90	19·30	<0·0001
Absolute gain (mm)	0·73	0·42	1·20	0·47	0·90	0·53	1·43	0·42	0·80	0·46	<0·0001
Absolute loss (mm)	0·30	0·53	0·58	0·60	0 50	0·72	0·60	0·50	0 34	0·55	<0·0001
Absolute net gain (mm)	0·43	0·58	0·62	0·60	0·40	0·70	0·83	0·58	0·46	0·59	<0·0001
Relative lumen pre	0·39	0·15	0·37	0·10	0·31	0·18	0·36	0·10	0·38	0·14	<0·0001
Relative lumen post	0·67	0·12	0·75	0·16	0·67	0·14	0·84	0·11	0·68	0·13	<0·0001
Relative lumen f-up	0·55	0·21	0·56	0·17	0·47	0·27	0·64	0·16	0·55	0·21	<0·0001
Relative gain	0·29	0·16	0·38	0·18	0·36	0·21	0·48	0·14	0·30	0·17	<0·0001
Relative loss	0·12	0·21	0·19	0·21	0·20	0·29	0·21	0·17	0·13	0·22	<0·0001
Net gain index	0·17	0·23	0·19	0·19	0·15	0·28	0·28	0·19	0·17	0·23	<0·0001
Loss index	0·51	3·99	0·52	0·75	0·73	1·61	0·44	0·37	0·51	3·75	0·34
Restenosis rates											
1. %DS ≥50% at f-up	36·3%		28·5%		50·9%		16·2%				<0·0001
2. Loss ≥gain/2	41·1%		45·0%		46·6%		35·4%				0·17
3. Loss ≥0·4 mm	31·5%		59·8%		38·1%		64·9%				<0·0001
4. %DS at f-up >0·9%DS pre	25·3%		16·1%		27·8%		9·2%				<0·0001

Restenosis definition 1=diameter stenosis ≥50% at follow-up; 2=loss ≥half the initial gain; 3=loss ≥0·4 mm (twice the post-PTCA variability of CAAS[39]); 4=recurrence of stenosis to within 10% of baseline severity. DCA=directional coronary atherectomy; Laser=excimer laser coronary angioplasty; Stent=Palmaz-Schatz stent; MLD=minimal luminal diameter; %DS=percent diameter stenosis; f-up=follow-up; pre=pre-intervention; post=post-intervention.

loss and relative lumen at follow-up were detected between the device groups, primarily due to significant differences between excimer laser coronary angioplasty and each of the other three groups (Table 3b, Fig. 2); for average directional coronary angioplasty/stent intervention, Palmaz-Schatz stent implantation was associated with less relative loss and greater relative lumen at follow-up than both excimer laser coronary angioplasty ($P<0·0001$) or directional coronary atherectomy ($P=0·01$), also, each of balloon angioplasty and directional coronary angioplasty were associated with late results that were superior to those of excimer laser coronary angioplasty ($P<0·0001$ and $P=0·005$, respectively). No significant difference in estimated outcome was observed between balloon angioplasty and either Palmaz-Schatz stenting or directional coronary angioplasty (Table 3b, Fig. 2). At the third predesignated level of comparison, thus after optimal intervention, inter-group differences were similar to the previous comparison and, in addition, balloon angioplasty was estimated to be associated with less relative loss and a greater relative lumen at follow-up than directional coronary angioplasty ($P=0·006$).

Influence of totally occluded lesions

Due to the greater prevalence of totally occluded lesions at baseline in the excimer laser coronary angioplasty group compared with the others (Table 2), particularly directional coronary atherectomy and Palmaz-Schatz stenting, multivariate analysis was repeated after excluding such lesions from all groups, to be certain that the observed differences could not be explained merely by this factor. Of the 24 successfully treated totally occluded lesions in the excimer laser coronary angioplasty group, nine (37%) had re-occluded at follow-up, compared with 59 of 286 (20%) in the balloon angioplasty group and none out of five in the Palmaz-Schatz stent group. Exclusion of totally occluded lesions at baseline from the population to be analysed resulted in no fundamental change in the findings of significant differences between devices in the influence of relative gain on outcome and in estimated outcome, as described.

Discussion

RESTENOSIS RATES

Criteria for angiographic restenosis were varied and this resulted in conflicting findings regarding late angiographic results. However, such disclosure is not new having been described many times in the past[30,47]. According to the widely used 'diameter stenosis ≥50%' criteria, Palmaz-Schatz stent implantation appeared to provide the best 6-month angiographic results and excimer laser coronary angioplasty the worst, with

Table 3 (a) Multiple linear regression model to evaluate the influence of vessel size, lesion location (LAD or not), lesion severity pre-intervention (relative lumen pre-intervention), relative gain and the device used for intervention, on each of relative luminal loss during follow-up (Rel Loss) and relative lumen at follow-up (RLFup). The influence of the device used is specifically investigated in two ways. First by examining whether the influence of the other independent parameters on the outcome parameters (Rel Loss and RLFup) varies between the four groups, by entering 'interaction terms', as explained in the methods section, and second, by comparing model-derived estimates of the outcome parameters between the four groups, at three nominal comparative levels, as also explained in the methods section (and given in Table 3(b)). In the Table below, vessel size has no independent influence on outcome (P=0·87), indicating that use of the relative measurements readily accounts for its known confounding effect[30]. LAD location is associated with a significant influence on outcome (P=0·03), with no apparent significant variation between devices, by analysis of variance (P=0·11). Relative gain and relative lumen pre-intervention exert highly significant influences on outcome (P<0·0001) and furthermore, a significant interaction is also detected between the device used and relative gain, indicating that the influence of luminal increase on outcome, varies significantly between the devices, which is elaborated by the 4 × 4 table immediately below

	Rel Loss (r^2=0·14)	RLFup (r^2=0·12)	*P*
Vessel size	0·00	0·00	0·87
LAD	0·02	− 0·023	0·03
Relative lumen pre-intervention	0·32	0·68	<0·0001
Relative gain	0·61	0·39	<0·0001
Device × relative lumen pre-intervention	—	—	0·23
Device × Vessel size	—	—	0·56
Device × LAD	—	—	0·11
Device × relative gain	—	—	0·02

Inter-group comparisons of the influence of relative gain

	Estimated RLoss	Estimated RLFup	PS	BA	DCA	ELCA
PS	0·59	0·41	—	0·98	0·10	0·07
BA	0·57	0·43	0·78	—	0·006	0·001
DCA	0·77	0·23	0·10	0·006	—	0·23
ELCA	0·86	0·14	0·07	0·001	0·23	—

Table 3 (b) Estimated relative loss and relative lumen at follow-up for each patient group, according to the 'centring' procedures performed, as described in the text, with inter-group comparisons using a 4 × 4 table (P values are not corrected for multiple comparisons), after:

(i) the 'average intervention': i.e. where a relative gain of 0·3 is achieved in a lesion with a relative lumen pre-intervention of 0·39, located in a 2·67 mm vessel. (Comparison of the estimates for the groups by analysis of variance reveals a significant difference at a level of *P*=0·0006)

	Estimated Rel Loss	Estimated RLfup	PS	BA	DCA	ELCA
PS	0·11	0·58	—	0·34	0·33	0·006
BA	0·13	0·55	0·34	—	0·80	0·002
DCA	0·13	0·55	0·33	0·80	—	0·02
ELCA	0·19	0·49	0·06	0·002	0·02	—

(ii) the 'average DCA/stent intervention': i.e. where a relative gain of 0·44 is achieved in a lesion with a relative lumen pre-intervention of 0·37, in a 3·12 mm vessel. (Comparison of the estimates for the groups by analysis of variance reveals a significant difference at a level of *P*<0·0001)

	Estimated Rel Loss	Estimated RLfup	PS	BA	DCA	ELCA
PS	0·18	0·62	—	0·14	0·01	<0·0001
BA	0·20	0·60	0·14	—	0·08	<0·0001
DCA	0·23	0·57	0·01	0·08	—	0·005
ELCA	0·31	0·49	<0·0001	<0·0001	0·005	—

(iii) the 'optimal intervention': i.e. where a relative gain of 0·61 is achieved in a lesion of 0·39 relative lumen pre-intervention located in a 3·2 mm vessel. (Comparison of the estimates for the groups by analysis of variance reveals a significant difference at a level of *P*=0·0007)

	Estimated Rel Loss	Estimated RLfup	PS	BA	DCA	ELCA
PS	0·28	0·72	—	0·73	0·01	0·0006
BA	0·30	0·70	0·73	—	0·006	0·0003
DCA	0·36	0·64	0·01	0·006	—	0·03
ELCA	0·47	0·53	0·006	0·0003	0·03	—

PS = Palmaz-Schatz stent; BA = balloon angioplasty; DCA = directional coronary atherectomy; ELCA = excimer laser coronary angiography.

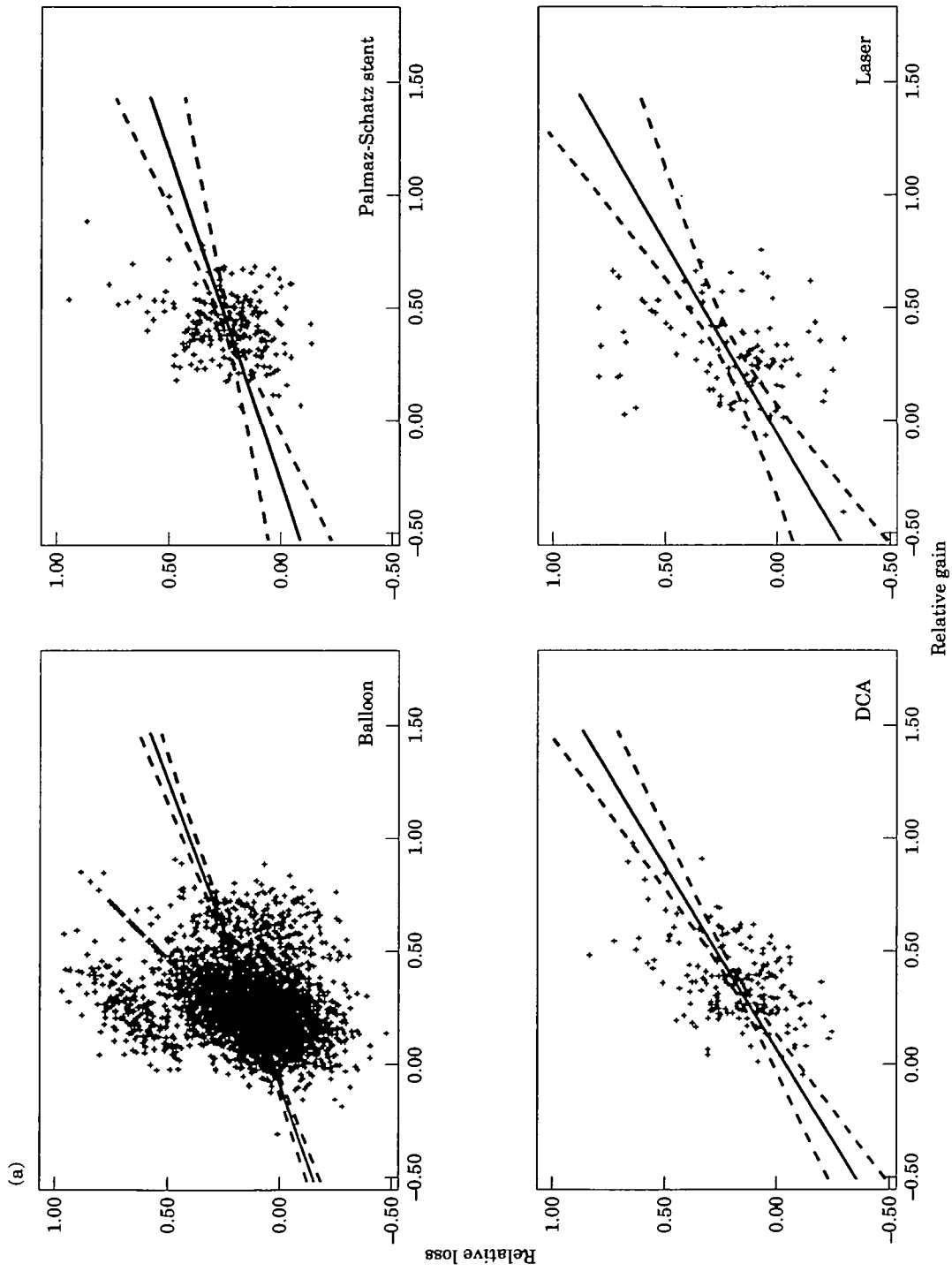


Figure 1 (a)

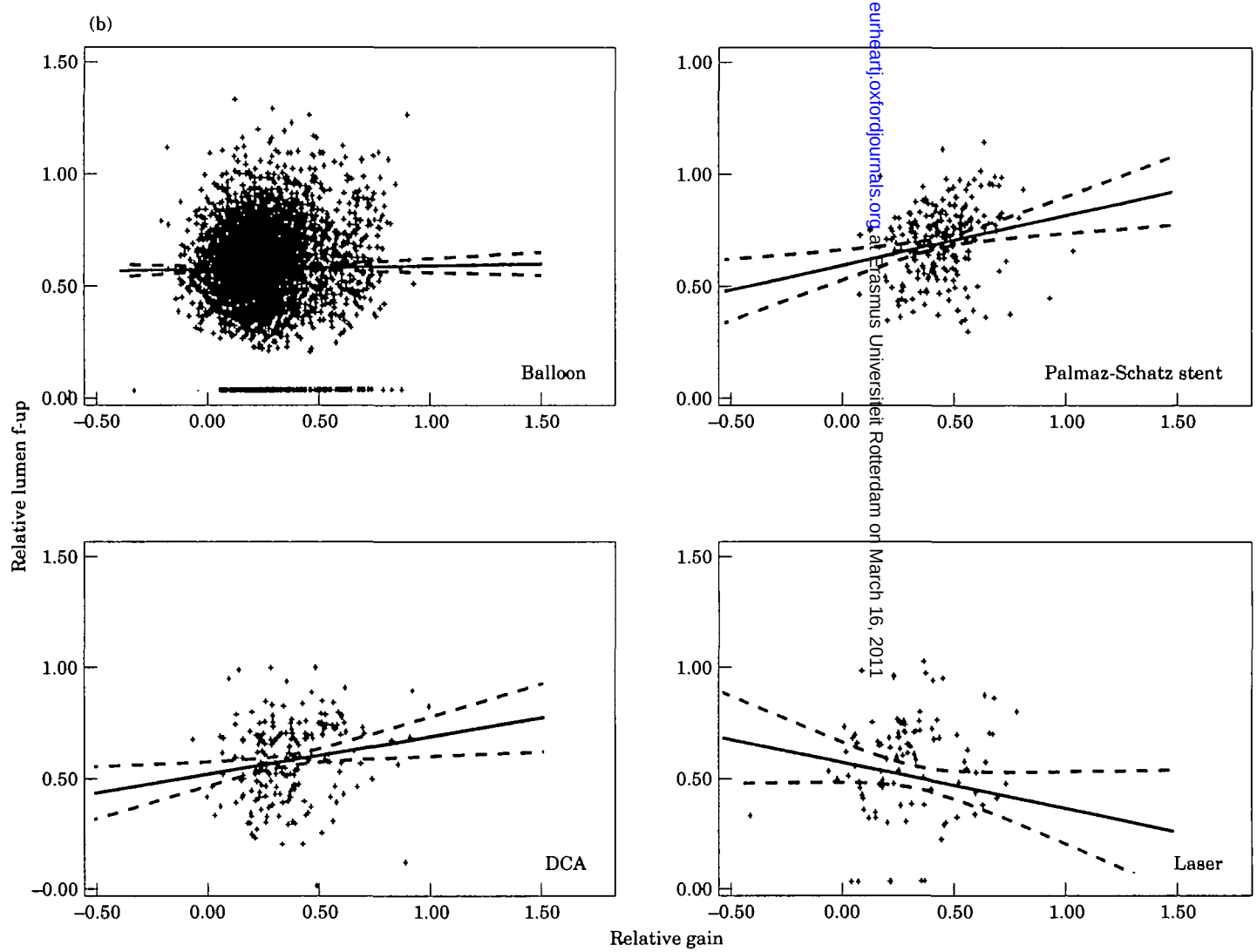


Figure 1 (b)

Figure 1 Scatter plots with simple linear regression analysis (and 95% confidence intervals), displaying the influence of relative gain (on the X axes) on each of relative loss (a) and relative lumen at follow-up (b) (on the respective Y axes). Significant differences are detected between the groups in the rate of the relative loss response to increasing relative gain (P=0·006) and in the relative lumen at follow-up response to relative gain (P=0·003). Balloon=balloon angioplasty; DCA=directional coronary atherectomy; laser=excimer laser coronary angioplasty.

balloon angioplasty and directional coronary atherectomy in between. These findings, although not providing any insight to the problem or a possible mechanistic explanation, concur well with the results of the more comprehensive multivariate analyses.

SIMPLE LINEAR REGRESSION — USEFUL BUT INCOMPLETE INFORMATION

In simple linear regression, the renarrowing response to increasing luminal enlargement was found to differ significantly between the groups, with the least favourable response displayed by the excimer laser coronary angioplasty group, whereby increasing relative gain was negatively associated with relative lumen at follow-up. The most favourable outcome was predicted for the Palmaz-Schatz stent group, with least increase in relative loss and greatest increase in relative lumen predicted at follow-up, with increasing relative gain. In addition, at the three levels of comparison chosen, excimer laser coronary angiography was associated with least favourable estimated outcome and Palmaz-Schatz stent the most favourable. These findings are strongly suggestive of differences between the device groups as regards the renarrowing response to luminal increase. However, because of the considerable differences in pre-procedural lesion severity, epicardial location and coronary vessel size between the groups and the known confounding effects of these factors on late angiographic outcome[10,14,26,27,42,44,48,49], emphatic conclusions would be premature without taking account of these factors in multiple linear regression.

LUMINAL RENARROWING AND LATE ANGIOGRAPHIC OUTCOME ARE INFLUENCED BY THE DEVICE USED

Multiple linear regression analysis confirmed the existence of significant differences between the devices with respect to the renarrowing response to luminal increase at intervention, independent of variations in vessel size, lesion severity or location and luminal increase at intervention. Retrospective exclusion of totally occluded lesions at baseline, on the grounds of significantly greater frequency in the excimer laser coronary angioplasty group, did not lead to any fundamental change in the differences found by multivariate analysis between excimer laser coronary angioplasty and the other three groups, or to improvement in the overall predictive power of the model (although some changes in the final model were detected). Accordingly, the discussion will focus on evaluation of the complete lesion populations, without this a priori stratification.

Evidence for device-specific influence on late angiographic results was twofold. Firstly, comparison of estimated angiographic results between devices at three pre-designated levels of intervention revealed significant differences, which became more apparent at increasing levels of relative luminal gain in larger vessel size (from the average to the optimal intervention). In particular, Palmaz-Schatz stenting and balloon angioplasty emerged with the most favourable predicted angiographic results in the selected circumstances. Late results of excimer laser coronary angioplasty were least favourable at each comparative level. Secondly, the influence of luminal increase on late results differed significantly between devices, whereby, for any given luminal increase significantly more favourable late angiographic results could be anticipated by balloon angioplasty, than by directional coronary angioplasty or excimer laser coronary angioplasty. These findings confirm our previous reports of inherent device-specific effects on the restenosis process and late angiographic outcome[9,15,23,27–29] and prompt questioning of the reported generalized model of restenosis after intervention[10,14,26], according to which, the device used for intervention exerts no independent influence on late angiographic results.

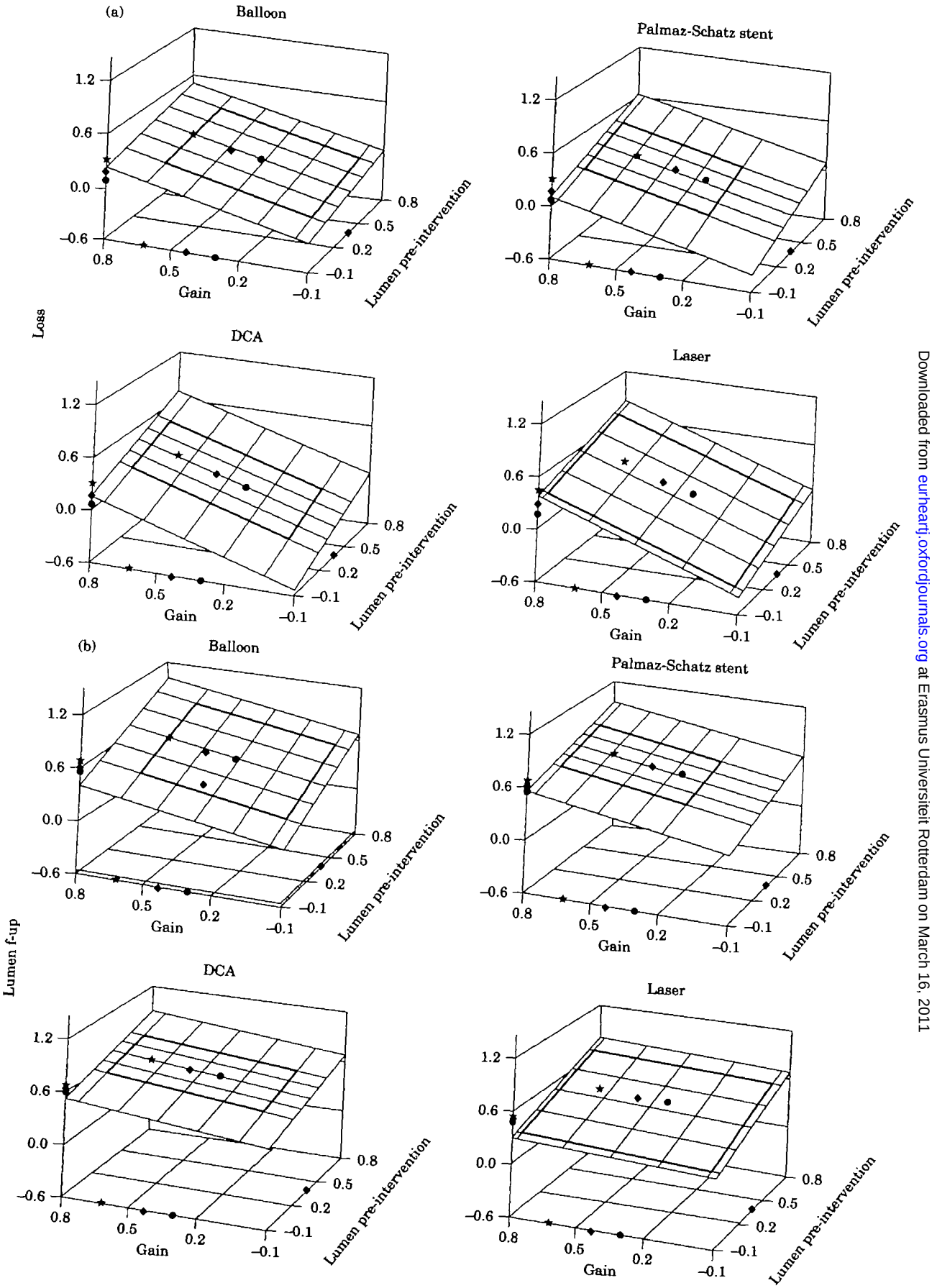
DIFFERENCES WITH PREVIOUS STUDIES

Although it is possible that differences in patient selection, demographic factors, interventional practices and quantitative angiographic methodology, may contribute to the differing findings between this and prior studies[10,14,26], three methodological variations may also potentially explain the conflict. Firstly, in previous studies, absolute coronary luminal measurements were employed and the wide differences in coronary vessel diameter between patient groups treated by different devices[10,14,26] may have exerted some confounding influence, according to our recent report of the influence of vessel size on late angiographic results[30]. A priori normalization of key angiographic parameters for vessel size in this study adequately controlled for this confounding influence. Secondly, prior studies did not specifically investigate potential differences between devices by considering so-called effect modification, by including interaction terms (as explained in the statistical paragraph), in the multivariate models. Accordingly, if such differences did actually exist (as we have found here), they would not have been detected. Thirdly, we used the multivariate model to allow additional and practically useful, if hypothetical, direct comparison of estimated outcome between devices, whereas previous studies constructed models to allow prediction of the likelihood of 'binary restenosis' from the post-procedural result, based on the multivariate findings[10,26].

CLINICAL IMPLICATIONS

(i) Optimization of the acute result

Although our findings, of an independent influence of the device itself on late interventional results, question the universal applicability of the previously reported generalized model of restenosis[10], in agreement with previous reports[7,9,10,26,27,30,48,50], we have also found that maximization of the acute result tends to provide more favourable late results. Accordingly, such an approach should be recommended as the practical goal



of all interventions (since it is predicted by our multivariate models that, depending on the device, 14%–43% of acute angiographic luminal increase will be retained as larger lumen at follow-up). By the same token, it must be acknowledged that such an approach does not actually prevent restenosis, but in fact provokes renarrowing, because 57%–86% of luminal increase (depending on the device) is subsequently 'lost' as luminal renarrowing. Ultimately, optimization of the acute result is not a conclusive solution to restenosis, merely creating a greater lumen to accommodate the inevitably greater degrees of subsequent renarrowing. Thus, the binary restenosis rate is perceptibly lower after stent implantation than balloon angioplasty, despite significantly greater measured luminal renarrowing (Table 2). Moreover, from our findings, it would appear that through systematic optimization of acute angiographic results, as has been previously recommended[7,9,10,26,27,30,48,50], differences in late angiographic outcome between devices become more apparent, thus, evaluation of current studies investigating the clinical value of optimal atherectomy and stent implantation will provide interesting ratification of the predictive models we have used. In fact, a recent comparison of atherectomy and balloon angioplasty in lesions matched for the acute procedural result, as well as baseline severity, has shown significantly superior late angiographic results by balloon angioplasty, supporting the findings of this study[27].

(ii) Implications for interpretation of the outcome of clinical trials and selection of devices for intervention

Since late angiographic results were predicted to be similar for Palmaz-Schatz stenting and balloon angioplasty in this study, the reported superior results after Palmaz-Schatz stenting compared with balloon angioplasty in both the BENESTENT and STRESS trials[24,25], may now be concluded to be simply a consequence of the greater acute luminal results achieved by stent implantation and not because of any difference in actual restenosis propensity. Accordingly, for two rapidly emerging practical reasons, stent implantation may soon be considered the device of choice above balloon angioplasty, when the choice exists. Firstly, stent implantation, with or without adjunctive balloon dilatation, can consistently achieve optimal luminal results, whereas balloon angioplasty alone clearly cannot and the hypothetical optimal intervention for balloon angioplasty is rarely observed. Secondly, studies with optimization of stent deployment[51,52] suggest that stringent anticoagulation, which carries the considerable side effect of bleeding complications[24,25] may no longer be required to combat the previously reported high risk of acute and sub-acute occlusion[21].

Since directional coronary atherectomy was associated with less favourable predicted late angiographic results than balloon angioplasty in this study, it could be speculated that in CAVEAT[7] and CCAT[8], its consistent achievement of greater acute luminal results adequately compensated for this apparently increased restenosis propensity, providing similar late angiographic results for directional coronary atherectomy as balloon angioplasty, as had been previously described by our group, in a comparison of matched coronary lesions[9]. Although optimization of the acute result by directional coronary atherectomy was predicted to provide improving late angiographic lumen in this study, as previously reported[6,26,27], the main concern raised here regarding directional coronary atherectomy is the greater propensity to restenosis, compared with balloon angioplasty and Palmaz-Schatz stenting. Namely, with comparable increase in relative luminal gain, if directional coronary atherectomy is used then 77% of the increase will subsequently be lost as luminal renarrowing, compared with 57% for balloon angioplasty and 59% for Palmaz-Schatz stenting, findings which, as previously mentioned, are in alignment with a recent comparative study[27]. The place of directional coronary

Figure 2 Three-dimensional graphic representations of the findings of multiple linear regression analysis (Table 3). Relative gain is represented on the X axis, increasing from right to left, relative lumen pre-intervention on the Z axis, increasing from front to back and each of relative loss (a) and relative lumen at follow-up (b) on the respective Y axes. For illustrative effect, the ranges of the regression planes are identical from right to left and from front to back. In addition, parallel lines are drawn through the mean and ± 1 and ± 2 standard deviations of the means of relative gain and relative lumen at follow-up for each device group. The true location of most (95%) of the lesions may thus be easily identified within each regression plane, by emphasizing these boundaries as shown. The greater frequency of total occlusions pre-intervention in the ELCA group is reflected by the close approximation of the outlined area with the entire regression plane. Generally, greater relative luminal increase at intervention in the Palmaz-Schatz stent group is reflected by location of the outlined area mainly in the left half of the plane. The slope of the regression planes from right to left represent the regression coefficient associated with relative gain for each device, as provided in Table 3a. Similarly, the slope of the planes from front to back reflect the regression coefficients associated with relative lumen pre-intervention, as given for each device. A significant difference in slopes from right to left can be appreciated, reflecting the findings in the models. Comparisons of outcome after 'centring' to the 'average intervention' (the circular dot), and for the 'average directional coronary atherectomy/stent intervention' (the diamond symbol) and the 'optimal intervention' (the star symbol) are illustrated. The position of each symbol in each regression plane represents the respective location of the relevant comparative level within each population (thus, for example, the point of 'average intervention' is located exactly in the centre of the balloon angioplasty and excimer laser coronary angiography regression planes, but somewhat below the centre in the directional coronary atherectomy and well below the centre in the Palmaz-Schatz stent regression planes, whereas optimal intervention is really located at the upper extremity of the balloon angioplasty plane, but still within one standard deviation of the mean in the Palmaz-Schatz stent plane). The vertical height of the symbol on each Y axis may be used to visually compare model-estimated outcome between devices, representing the values provided in Table 3b. Balloon = balloon angioplasty; DCA = directional coronary atherectomy; Laser = excimer laser coronary angioplasty; Loss = relative luminal loss; Gain = relative luminal gain; Lumen f-up = relative lumen at follow up.

Table 4 (a) Repeat multiple linear regression analysis, after exclusion of totally occluded lesions pre-intervention. Format is similar to Table 3. No fundamental differences in results obtained are observed

	Rel Loss (r^2=0·14)	RLFup (r^2=0·12)	*P*
Vessel size	0·00	0·00	0·31
LAD	0·02	−0·02	0·0009
Relative gain	0·70	0·03	<0·0001
RLumen pre-intervention	0·23	0·77	<0·0001
Device × RG			

Inter-group comparison of the influence of RG on outcome

	Estimated RLoss	Estimated RLFup	PS	BA	DCA	ELCA
PS	0·56	0·44	—	0·85	0·20	0·03
BA	0·59	0·41	0·85	—	0·03	0·008
DCA	0·77	0·23	0·20	0·03	—	0·48
ELCA	0·89	0·11	0·03	0·008	0·48	—

Table 4 (b)

(i) the 'average intervention': i.e. where a relative gain of 0·28 is achieved in a lesion with a relative lumen pre-intervention of 0·41, located in a 2·67 mm vessel. (Comparison of the estimates for the groups by analysis of variance reveals a significant difference at a level of P=0·06)

	Estimated R Loss	Estimated RLfup	PS	BA	DCA	ELCA
PS	0·12	0·57	—	0·65	0·47	0·04
BA	0·13	0·55	0·65	—	0·57	0·008
DCA	0·13	0·55	0·47	0·57	—	0·09
ELCA	0·18	0·51	0·04	0·008	0·02	—

(ii) the 'average DCA/stent intervention': i.e where a relative gain of 0·43 is achieved in a lesion with a relative lumen pre of 0·37, located in a 3·14 mm vessel. (Comparison of the estimates for the groups by analysis of variance reveals a significant difference at a level of P=0·001)

	Estimated R Loss	Estimated RLfup	PS	BA	DCA	ELCA
PS	0·18	0·62	—	0·06	0·02	0·0001
BA	0·21	0·59	0·06	—	0·34	0·002
DCA	0·23	0·57	0·02	0·34	—	0·06
ELCA	0·29	0·51	0·001	0 002	0·02	—

(iii) the 'optimal intervention': i.e where a relative gain of 0·61 is achieved in a lesion with a relative lumen pre of 0·29, located in a 3·2 mm vessel. (Comparison of the estimates for the groups by analysis of variance reveals a significant difference at a level of P=0·003)

	Estimated R Loss	Estimated RLfup	PS	BA	DCA	ELCA
PS	0·28	09·72	—	0·03	0·02	0·0006
BA	0·34	0·66	0·03	—	0·39	0·009
DCA	0·37	0·63	0·02	0·39	—	0·06
ELCA	0·47	0·53	0·006	0·009	0·06	—

atherectomy in the interventional armamentarium, thus, remains to be finally clarified.

It would be foolhardy to suggest that there is no place for laser technology in interventional cardiology, based on the findings of this study, since the technology and application methodology is continuously evolving. In addition, its value in initially recanalizing unfavourable lesions has been well documented[12,53]. However, the 37% reocclusion rate following recanalization of total occlusions by excimer laser coronary angioplasty in this study and the unfavourable late angiographic results in multivariate analysis, compared with the other devices,

are not encouraging for the particular approach employed in the patients described in this study (which was the conventional therapy during the period 1991–93). Newer treatment applications, such as use of continuous local saline infusion during laser ablation, as well as changing technology, may bring improved long-term results. In addition, combination therapy of successful recanalization of occluded vessels by laser technology followed by optimization of the result by stent implantation is a potentially interesting area which remains to be clinically explored.

POTENTIAL MECHANISTIC EXPLANATIONS FOR DIFFERENCES IN PREDICTED OUTCOME BETWEEN THE DEVICES

Differences in distribution of influence of clinical or angiographic morphological factors between the patient groups may theoretically influence outcome, but previous studies, including such variables, have not shown any major confounding effects, which might distort the relationships demonstrated between the angiographic parameters on which this study has been concentrated[9,10,26,27,42,44,48,49,54]. In particular, a recent comparison of late clinical and angiographic outcome among our patients with stable and unstable angina treated by directional atherectomy revealed no significant difference in restenosis tendency[55]. Furthermore, the greater frequency of total occlusion at baseline in the excimer laser coronary angioplasty and balloon angioplasty groups in this study did not unduly influence the findings. Accordingly, we have focused on the principal quantitative angiographic factors which are known to exert fundamental influence on late angiographic results.

(i) Rheological considerations — chronic recoil and vessel remodelling

It must be stated at the outset that any mechanistic attempt to explain the observed differences in predicted outcome would be somewhat speculative and is not based on the findings of this study, but rather represents an attempt to understand the findings of this study, in the light of current knowledge and emerging findings of ongoing investigations. Our hypothesis, based on experimental, pathological and ultrasound evidence, is that since the mode of vessel wall injury imparted by the different devices appears to be considerably different, the 'rheo-fibroproliferative' response of the vessel also differs significantly, between lesions treated by different devices. In the first place, it is already known that acute elastic recoil, which is an inherent feature of balloon angioplasty[56–58] and thus also excimer laser coronary angioplasty, is partially reduced by directional coronary atherectomy[59] and virtually abolished by Palmaz-Schatz stenting[17]. Consequently, if chronic elastic recoil and late vessel remodelling are confirmed as important factors in late luminal renarrowing[60–63], it would be expected that devices with differing rheological effects would produce differing late outcome, despite apparently similar acute angiographic results (thus similar acute luminal increase, in apparently angiographically similar lesions, could conclude in considerably different late angiographic results, as has been found by our multivariate models in this study).

(ii) Fibro-proliferative aspects of intimal response due to device-specific injuries

Secondly, if the major non-elastic component of renarrowing is fibroproliferative neointimal hyperplasia and if this is proportional to the degree of injury imparted during intervention[64], it seems logical that device-specific injuries may provoke particulate response levels. Ablation of tissue by excimer laser coronary angioplasty, with generation of shockwaves[65] and of vapour bubbles[66], can cause extensive intimal dissection, medial necrosis and internal elastic lamina abrasion[66,67] and ultraviolet radiation may be somewhat mutagenic[68]. Similarly, excision of vessel wall components, with exposure of intramural tissue[5,6,48], as well as plaque fracture, compression and vessel stretching by directional coronary angioplasty[3,4], might create greater injury to the vessel wall than the plaque fracture, compression and vessel stretching caused by balloon angioplasty[3,4,5,69–71]. Stent implantation presupposes some of the features of balloon injury, but modified by creation of a larger lumen of a mainly smooth and circular contour, which may reduce turbulence and shear stress[18–20]. Accordingly, it seems reasonable to speculate that these mechanistic differences may, at least partly, explain the observed differences in predicted restenosis propensity and late angiographic outcome between the devices studied here.

LIMITATIONS

First, although most of the patients evaluated in this study were recruited during major multicentre randomized trials and overall quantitative angiographic follow-up was 93% of eligible patients, this is ultimately an observational study and final outcome certainly requires verification through similar evaluations in randomized comparisons of interventional devices. Second, it could be argued that specific lesion morphological indications for the use of the four devices may differ considerably and so influence late results. However, we have previously demonstrated that the principle angiographic determinants of late angiographic outcome after coronary intervention are the quantitative angiographic parameters included in this study[9,27,42,44,48,49]. Third, according to current interventional practice today, the post-procedural results of directional coronary atherectomy and stent implantation might not be considered optimal and the paucity of lesions with super-optimal results may have affected the reliability of the model in predicting late angiographic results for each device after optimal intervention. Nevertheless, these angiographic data are comparable with those obtained in STRESS, BENESTENT, CAVEAT and CCAT[7,8,24,25], and are thus representative of diverse multinational experience. Fourth, focusing on angiographic parameters does not take account of potentially confounding effects of

clinical factors, but, as previously stated, prior studies have demonstrated no distortion of angiographic relationships, when clinical factors are included, so we feel justified here in concentrating on key angiographic parameters.

Conclusion

Definite differences in restenosis propensity were detected between patient groups treated by Palmaz-Schatz stent implantation, directional atherectomy, balloon angioplasty and excimer laser coronary angioplasty, independent of variations in lesion severity and location, vessel size and luminal increase. Interestingly, lesions treated by balloon angioplasty or Palmaz-Schatz stent implantation (predominantly dilating) were associated with more favourable angiographic profiles than directional atherectomy or excimer laser (mainly debulking). These differences, which may represent inherent device-specific characteristics of the rheo-fibroproliferative response to unique vessel wall injury, require further study in large patient groups, ideally with optimal interventional strategies and intravascular ultrasound evaluation, for corroboration and possible mechanistic explanation.

This study would not have been possible without the patients who willingly agreed to participate in the multicentre trials, the clinical collaboration of multiple centres throughout Europe, as well as in North and South America and the reliable quantitative coronary angiographic analysis and database management at the angiographic core laboratory at Cardialysis, Rotterdam.

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