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Intravascular ultrasound evaluation after sirolimus eluting stent implantation for de novo and in-stent restenosis lesions

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Aims The aim of this study is to compare the efficacy of sirolimus-eluting stents (SES) on neointimal growth and vessel remodelling for in-stent restenosis versus de novo coronary artery lesions using serial intravascular ultrasound (IVUS).
Methods and results The study population consisted of 86 patients with in-stent restenosis (ISR) (*n*=41) or de novo lesions (*n*=45) treated with SES and evaluated by IVUS post-procedure and at follow-up. One 18-mm SES was used for de novo lesions while 16 patients with ISR received >1 SES (total stented length 17.9 mm vs 22.0 mm respectively; *P*=0.004). At follow-up, no differences were observed between the ISR and de novo groups with respect to changes in the mean external elastic membrane (1.7% vs 1.3%; *P*=0.53), plaque behind the stent (1.2% vs 3.4%; *P*=0.49), and lumen areas (0.7% vs 1.9%; *P*=0.58). No positive remodelling or edge effect was observed. A gap between stents was observed in two patients with ISR, where more prominent, though non-obstructive, neointimal proliferation was noted.
Conclusion Sirolimus-eluting stenting is equally effective at inhibiting neointimal proliferation in de novo and ISR lesions without inducing edge restenosis or positive vascular remodelling.

Introduction

Coronary stenting has reduced restenosis compared with balloon angioplasty; however stent restenosis is still a major problem in interventional cardiology.[1–3] Intracoronary radiation has emerged as an effective treatment for restenosis after coronary stent implantation.[4–6] However, the widespread use of intracoronary radiation therapy is limited by considerable logistic requirements, and potential side effects such as edge effects, geographic miss, delayed healing and late thrombosis.[7–9]

Recently, sirolimus-eluting stents (SES) have been demonstrated to significantly reduce late luminal re-narrowing after coronary intervention, both for de novo lesions[10,11] and for in-stent restenosis (ISR).[12,13]

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This favourable effect is accomplished by a potent and sustained inhibition of neointimal tissue growth by the anti-proliferative drug applied to the stent in a polymer. However, the treatment of ISR with placement of a new, drug-eluting stent presents different challenges compared to the treatment of de novo lesions. The repeat stent implantation has to be performed in the presence of a previously placed stent obstructed by soft neointimal tissue. ISR lesions have different histological features and proliferation profiles from the de novo lesions.[14] In an animal re-injury model, it has been shown that the accumulation of extracellular matrix is a major factor in repeat restenosis formation and the cellular content in the vessel wall is different from that observed in de novo lesions.[15,16] Therefore, ISR lesions may respond differently from de novo lesions, particularly since this represents a second episode of barotraumas to the vessel.[17] Although SES have been shown to be effective at inhibiting neointimal hyperplasia (NIH) in both de novo[11,18] and ISR[12,13] lesions, the influence of SES on vascular remodelling and edge effects have not previously been evaluated in patients with ISR.

The aim of this study is to compare the vessel responses of de novo and ISR lesions treated with SES implantation, as assessed by serial volumetric intravascular ultrasound (IVUS).

Methods

Patient population

Patients with either de novo coronary lesions or ISR assigned to receive sirolimus eluting stent in the respective First-In-Man (FIM) registries were compared.[11,18] In the FIM de novo group, eligible patients had stable or unstable angina or documented silent ischaemia, with a single de novo lesion of a native coronary artery in a vessel between 3.0 and 3.5 mm in diameter that could be covered by a single 18 mm stent. In the FIM ISR group, patients with ISR in a native coronary artery and objective evidence of ischaemia were included. The vessel size had to be >2.5 mm and <3.5 mm. In-stent restenosis in saphenous vein grafts was excluded.

All lesions were predilated before implantation of a sirolimus-eluting Bx VELOCITY™ stent (Cordis Waterloo, BL) using conventional techniques. All ISR patients and 30 of 45 patients from the FIM de novo group received the slow release formulation SES. Fifteen patients in the FIM de novo trial received the fast release formulation SES. All stents were 18 mm long and 2.5–3.5 mm in diameter.

All patients received aspirin (325 mg/day, indefinitely) and clopidogrel as a 300 mg loading dose immediately after stent implantation followed by 75 mg/day for 2 months in patients with de novo lesions and 2 to 4 months, according to discretion of the operator, in the ISR patients.

IVUS analysis and quantitative measurements

Intravascular ultrasound imaging was performed after administration of intracoronary nitroglycerin (150–200 μg) using motorized catheter pullback at a speed of 0.5 mm/s. Ultrasound images were recorded on s-VHS tape for off-line analysis. The lumen, stent, and external elastic membrane contours were detected with the CURAD QCU analysis software (Curad BV, Wijk Bij Duurstede, The Netherlands) applying 3-D reconstruction of the stented segment, as described elsewhere.[19] Quantitative IVUS analysis included the stent segment and the coronary segment beginning 5 mm proximal to and extending 5 mm distal to the stented segment. Lumen, stent boundaries and external elastic membrane were detected using a minimum cost algorithm. Mean external elastic membrane area (EEMA), stent area (SA) and lumen area (LA) were calculated. Mean total plaque area (TPA), mean plaque behind stent area (PBSA) and neointimal hyperplasia area (NIHA) were calculated as 'EEMA minus LA', 'EEMA minus SA', 'SA minus LA', respectively.

Delta values (Δ) for each measurement were calculated as follow up minus post- procedure. To eliminate the influence of the vessel size and the length of the analysed segment, which affects area calculations, percent change [(Δarea/post-procedure area)*100] was also calculated.

Incomplete stent apposition (ISA) was defined as one or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut.[20]

Qualitative analysis was performed by reviewing all post-procedure and follow-up IVUS videotapes to identify the ISA.

Table 1 Patient demographics[a]

	De novo (*n*=45)	ISR (*n*=41)	*P* value
Age	57.4±11	57.8±12	0.87
Male, %	69	80	0.48
Hypertension, %	49	63	0.17
Diabetes mellitus, %	16	27	0.19
Hypercholesterolaemia, %	62	71	0.40
Smoking, %	58	56	0.87
Previous MI, %	29	56	0.01
Unstable angina, %	40	27	0.19
Treated vessel			
LAD, %	53	39	0.13
CX, %	20	22	0.51
RCA, %	27	39	0.25

[a]Abbreviations. ISR: in-stent restenosis; MI: myocardial infarction; LAD: left anterior descending artery; CX: circumflex artery; RCA: right coronary artery.

Quantitative coronary angiographic analysis

Serial coronary angiography was performed at baseline (before and after intervention) and at 4 or 6-month follow-up. In-stent stenosis was defined as >50% diameter stenosis (DS) at follow-up. Quantitative angiographic analysis was performed by an independent core laboratory (Brigham and Women's Hospital, Boston, Mass).

Statistical analysis

Statistical analysis was performed using the SPSS software (version 10.0, Statistical Package for the Social Sciences, Chicago). Continuous variables are presented as mean±SD and compared using paired or unpaired Student's t test, as appropriate. Categorical variables are presented as counts and frequencies and compared using chi-square test or Fisher's exact test. Intravascular ultrasound parameters among diabetics and non-diabetics with de novo or ISR lesions were analysed using one-way analysis of variance (ANOVA) and post hoc comparisons

Table 2 Quantitative coronary angiographic results[a]

	De novo (*n*=43)	ISR (*n*=40)	*P* value
Reference diameter, mm	2.94±0.38	2.74±0.3	0.015
Pre-procedure MLD, mm	0.96±0.35	0.87±0.44	0.35
Pre-procedure DS, %	67.3±11.3	67.8±15.8	0.86
Post-procedure (in-stent) MLD, mm	2.89±0.35	2.66±0.33	0.003
Post-procedure (in-stent) DS, %	3.27±7.37	3.66 ±9.9	0.83
Follow-up (in-stent) MLD, mm	2.82±0.38	2.54± 0.58	0.009
Follow-up (in-stent) DS, %	6.04±6.8	8.8±17.8	0.34
Late loss (in-stent), mm	0.07±0.30	0.12±0.41	0.50

MLD; minimal lumen diameter, DS; diameter stenosis.

[a]Values are mean±SD.

Table 3 Serial intravascular ultrasound measurement[a]

	De novo (*n*=43)	ISR (*n*=37)	*P* value
Post-stent implantation			
Stent length, mm	17.9±1.2	22.0±7.6	0.004
EEM mean area, mm^2	16.4±4.4	16.5±4.1	0.9
PBS mean area, mm^2	9.1±3.3	9.3±2.9	0.76
Lumen mean area, mm^2	7.4±1.6	6.9±1.7	0.19
Stent mean area, mm^2	7.4±1.6	6.9±1.7	0.17
Minimum lumen area, mm^2	6.1±1.6	5.5±1.6	0.41
Follow-up			
Stent length, mm	18.2±1.2	22.5±10.3	0.015
EEM mean area, mm^2	16.7±4.1	16.6±3.9	0.93
PBS mean area, mm^2	9.1±3.1	9.4± 2.6	0.72
Lumen mean area, mm^2	7.6±1.9	7.1±1.9	0.21
Stent mean area, mm^2	7.7±1.8	7.2±1.9	0.21
Minimum lumen area, mm^2	6.1±1.8	5.6±1.7	0.51
NIH mean area, mm^2	0.03±0.06	0.05±0.12	0.33
% Area obstruction	0.4±0.7	0.8± 2.1	0.21
Area change at follow-up			
% Lumen mean area	0.7±8.3	1.9±10	0.58
% EEM area	1.7±7.1	1.3±7.4	0.53
% PBS area	1.2±11.6	3.4±11.4	0.49

ISR; in-stent restenosis, EEM; external elastic membrane, PBS; plaque behind the stent, NIH; neointimal hyperplasia.

[a]Values are mean±SD.

were made with the Tukey–Kramer HSD (honestly-significant-difference) test for multiple group comparisons. Multivariate linear regression analyses were performed to evaluate the independent value of baseline and procedural variables in predicting the IVUS outcomes at follow-up. All variables presented in Table 1, Table 2, and Table 3 were tested and the final models were built by stepwise selection, with probabilities for entry and removal of factors set to 0.05 and 0.10, respectively. All tests were two-tailed and a *P* value <0.05 was considered as statistically significant.

Results

Patient demographics are shown in Table 1. In the ISR group, four patients had failed previous brachytherapy treatment, 11 patients had recurrent percutaneous coronary interventions and three patients had totally occluded vessels before SES implantation. In the de novo group, all patients had one SES but in the ISR group, 16 of 41 patients received more than one stent (range:2–5 stents). The mean length of predilation balloons was 17.9±4.2 mm in the ISR group, and 17.9±3.1 mm in de novo group. Longer than 20 mm balloon was not used in any case and 44% of the balloons used for predilation were =16 mm.

Follow-up cardiac catheterization was performed at 4 months (*n*=30) or 6 months (*n*=13) in the de novo group and at 4 months (*n*=40) in the ISR group. Baseline, post-procedure, and follow-up angiographic characteristics are shown in.Table 2 When compared to the de novo group, the ISR group showed smaller reference vessel diameters, as well as post-procedure and follow-up minimal lumen diameters (MLD). However, follow-up% DS and late loss was not different there was not a significant difference between post-procedure and follow-up MLD in either the de novo or ISR patients.

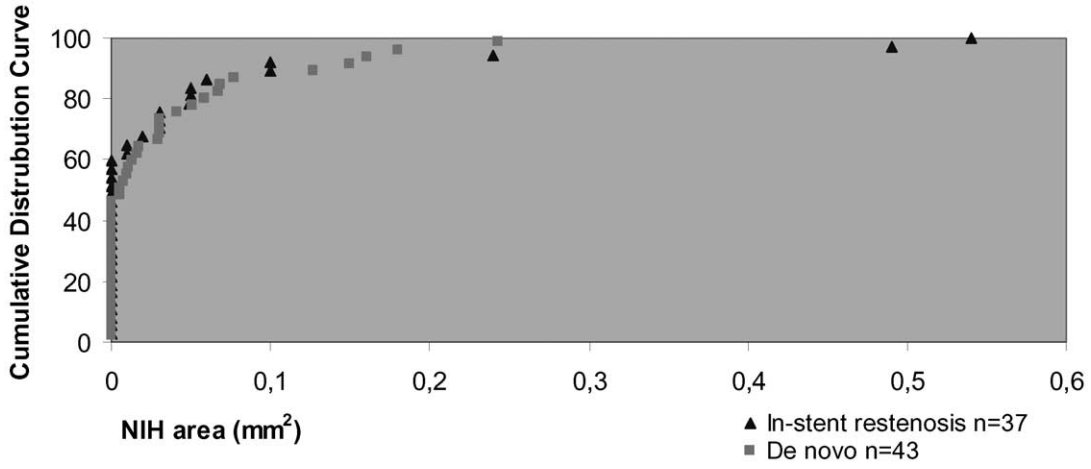

Fig. 1 Cumulative distribution curve of neointimal hyperplasia (NIH) area at follow-up for the patients with in-stent restenosis and de novo coronary lesions.

Table 4 Intravascular ultrasound measurements at the edge segments

	Lumen area (mm^2)			Plaque area (mm^2)			EEM area (mm^2)		
	Post	Follow-up	*P*-value[a]	Post	Follow-up	*P*-value[a]	Post	Follow-up	*P*-value[a]
Proximal edge									
De novo	9.1±3.0	8.8±3.4	0.17	6.8±2.8	6.9±2.9	0.42	15.9±4.1	15.7±4.4	0.57
ISR	7.3±2.1	7.7±2.5	0.13	7.9±3.1	8.1±3.3	0.56	15.2±3.6	15.8±3.9	0.14
P-value[b]	0.005	0.29		0.08	0.75		0.53	0.12	
Distal edge									
De novo	7.6±2.5	7.8±3.0	0.53	5.0±2.4	5.1±2.2	0.79	12.6±3.9	12.9±4.3	0.40
ISR	7.0±2.3	7.2±2.4	0.34	6.1±3.6	5.9±3.5	0.69	13.1±5.1	13.2±4.9	0.71
P-value[b]	0.37	0.44		0.21	0.14		0.71	0.64	

Post; post procedure, FU; follow-up, ISR; in-stent restenosis.

[a] *P*-value; post-procedure vs follow-up.
[b] *P*-value; de novo vs in-stent restenosis.Values are mean±SD.

Table 3 shows post-procedure and follow-up IVUS results. Serial IVUS was performed in 43 of 45 patients with de novo coronary lesions and 37 of 41 with ISR lesions. The total stented length was longer in the ISR group than in the de novo group. No differences were found between the two groups with respect to mean EEMA, SA, LA, and PBSA, both post-procedure and at late follow-up.

External elastic membrane and PBS area measurements showed no significant changes between the two periods, in patients with ISR or de novo lesions. There was also no significant difference in NIH area at follow-up (Fig. 1). Two patients in the ISR group had a gap between two stents and these patients had increased NIH in the gap segment.

Late acquired ISA was not observed at 4 months in any studied patient. Two patients (one in the de novo and one in the ISR) showed persisting ISA at late follow-up. Intravascular ultrasound analyses were performed in 16 (seven from de novo, nine from ISR group) out of 18 diabetic patients. There was no significant difference between diabetics and non-diabetics with respect to in-stent mean NIH area (0.07 mm^2 vs 0.04 mm^2, *P*=0.24). Also, there was no difference in the mean percent area obstruction among diabetics with de novo and with ISR, and non-diabetics with de novo and with ISR (0.4% vs 1.6% vs 0.5% vs 0.7%, respectively; *P*=ns by ANOVA). Serial edge segment analysis was possible at 34 distal and 24 proximal edges in the ISR group and at 37 distal and 39 proximal edges in the de novo group, respectively. Edges were excluded from analysis when there was a side-branch take off within 5 mm of the stent, inadequate image quality or incomplete image acquisition. Table 4 shows post-procedure and follow-up IVUS findings for edge segments. No significant difference was observed at follow-up in the de novo or ISR groups. There was no significant difference in lumen area changes between patients with and without diabetes mellitus both at the proximal (+0.3 mm^2 vs −0.2 mm^2 *P*=ns) and the distal edges (+0.3 mm^2 vs +0.2 mm^2 *P*=ns).

Multivariate regression analyses have identified post-procedure lumen area to be high correlated and to be the only independent predictor of follow-up IVUS mean

lumen area (coefficient 0.90; *P*-value <0.001; r^2 of the model 0.84). Importantly, neointimal area and mean percent area obstruction at follow-up could not be predicted by any the tested variables.

Clinical follow-up

Clinical follow-up of patients with de-novo and ISR have been previously presented in detail.[11,18,35] Briefly, in the de-novo group, one patient died (in hospital; cerebral haemorrhage), one patient developed non-Q myocardial infarction and two patients underwent target vessel revascularization. No patient presented with in-stent restenosis and major adverse clinical events (death, cerebrovascular accident, myocardial infarction, or re-intervention) free survival was 91% at 2 years follow-up. In the ISR group, two patients died (one sudden death, one due to congestive heart failure), one patient, who had received 5 SESs, showed no late lumen loss at 5 months follow-up, but developed an inferior myocardial infarction 7 months after the index procedure. Only two patients presented with in-stent restenosis were asymptomatic. Therefore, repeat revascularization was not performed. Adverse clinical events free survival was 92.7% after 1 year.

Discussion

In the present study we report for the first time a comparative analysis of the effects of sirolimus-eluting stent implantation in patients with de novo lesions versus those with in-stent restenosis, as evaluated by serial angiographic and volumetric intravascular ultrasound. We observed that: (1) SES were equally and highly effective at preventing neointimal proliferation in both de novo and ISR lesions, (2) no significant changes were observed in external arterial dimensions between immediately post-procedure and late follow-up in patients with de novo or ISR lesions, (3) SES were equally effective at inhibiting NIH in diabetics and non-diabetics in both groups (4) late acquired incomplete stent apposition was not observed at 4 or 6 month follow-up in either group of lesions.

The restenotic and de novo atherosclerotic lesions differ considerably between each other, reflecting the distinct physiopathological background involved in both situations.[16] Moreover, re-dilatation of restenotic lesions (i.e. exposure to 'double injury') is associated with a peculiar local vascular response, distinct from that observed after the first dilatation.[17] Accordingly, in practice treatment of restenotic lesions presents a different behaviour as compared to de novo lesions. Late luminal re-narrowing had been observed to be consistently more frequent after treatment of restenotic than of de novo lesions, with re-restenosis rates >70% in its most severe forms.[3,21] Several pharmacological and mechanical treatment modalities have shown disappointing results for the prevention and treatment of restenosis. So far, vascular brachytherapy is the only therapy proven in randomized clinical trials to be effective for the treatment of ISR, although post-brachytherapy failures have been reported to occur in up to 30–40% of cases.[21,22] After brachytherapy for ISR, the late lumen loss was observed to range from 0.38 to 0.64 mm in studies with either γ or β radiation.[6,23,24] However, late lumen loss after SES implantation for ISR was 0.12 mm, the amount of NIH close to zero (0.05 mm^2) and lumen area obstruction at IVUS examination was only 0.8%. Notably, in our series SES implantation equalized the IVUS-assessed NIH between de novo and ISR lesions. Interestingly, as SES had virtually eliminated NIH post-procedure and follow-up mean lumen areas were almost the same, which explains the high correlation observed between these two parameters. Furthermore, since NIH was almost eliminated in all patients, IVUS neointimal area and percent lumen area obstruction at follow-up had an almost uniform value close to zero in all included cases, which may justify the absence of predictive value for all tested characteristics.

Concerns have been raised whether SES could significantly affect the vascular architecture behind the stent struts, as previously reported following coronary radiation.[25–27] However, in our series no significant vessel enlargement was observed in either de novo or in-stent restenotic lesions. Indeed, the percent change in vessel area in both de novo (1.7%) and in ISR (1.3%) after SES implantation was highly comparable to that previously reported after bare metal stent implantation (2%).[28]

'Edge effect', or restenosis at the stent margins, has occurred most notably with radioactive stents, as a combined effect of radiation dose fall-off and vessel injury outside the stent.[29–31] IVUS analysis of edge stenosis with radioactive stents has shown that this results predominantly from negative remodelling with exaggerated neointimal hyperplasia. In our series, no 'edge effect' was observed. In both de novo and restenostic lesions, the luminal dimensions were maintained at both stent edges, which is in accordance with the IVUS findings of the RAVEL trial, where a trend toward larger lumen areas at distal edge was reported. The possible reasons for more beneficial effect of the drug at the distal edge might be a higher downstream concentration of the drug.

Diabetic patients have higher restenosis and recurrent ischemic event rates than non- diabetics even with aggressive revascularization strategies.[3] With serial IVUS Kornowski *et al.*[32] demonstrated that late loss following angioplasty among diabetics is predominantly due to exaggerated NIH. However, in our study, SES had virtually equalized the degree of NIH growth in patients with and without diabetes. Percent area obstruction did not differ among diabetics and non-diabetics, both in the de novo (0.4% vs 0.5%, *P*=ns) and ISR groups (1.6% vs 0.7%, *P*=ns). Our data are similar with the observations in the diabetic subgroup of the RAVEL trial, which demonstrated almost no NIH growth after SES implantation for de novo lesions (0.08 mm late lumen loss), with no binary restenosis occurrence (personal communication of A. Abizaid, MD PhD 2002).

Late acquired incomplete stent apposition (LAISA) is another potential concern with drug- eluting stents,[20] and recently published data have demonstrated that in

bare stents is due to positive vascular remodelling.[33] Although post-procedure ISA persisted in two patients at 4 month follow-up, no LAISA was observed in either the de novo or ISR groups in the present study. This is consistent with our quantitative IVUS measurements which showed no significant vessel size change at follow-up as well as and in the amount of plaque behind the stent. These findings suggest that the therapeutic effect of SES is solely due to inhibition of NIH without inducing positive vascular remodelling in either de novo or ISR lesions.

Apart from the well-known high rates of recurrence after treatment of ISR lesion, length (and the stented length) has been identified as one of the most important predictors of restenosis.[34,35] In the current study, the ISR group had a longer stented segment than the de novo lesion group. Nevertheless, the amount of NIH did not significantly differ between de novo lesions, treated with shorter stented lengths, and ISR in which multiple stents were more often implanted. Interestingly, in two patients with ISR, NIH was observed to be limited to the site of a gap between two stents. Taken together, these findings suggest that the therapeutic power of SES, is not adversely affected by the length of the stented segment as long as there is not a gap left between two adjacent stents during the index procedure.

Study limitations

This is a non-randomized comparison of sirolimus-eluting stents and the current report is limited as only the data from single de novo and relatively less complex ISR lesions in vessels with a diameter between 2.5 and 3.5 mm were enrolled. Therefore, results need to be confirmed by randomized trial with larger series of patients. The results in the diabetic subgroup are remarkable. However, due to the relatively small number of patients some of the interpretations may be highly speculative and may or may not be borne out in larger studies. Mid-term IVUS evaluation was performed at different time-points, at 4 months ('São Paulo cohort') or at 6 months ('Rotterdam cohort'). Nonetheless, no major differences in NIH were detected throughout the follow-up period, indicating that mid-term 4-month and 6-month IVUS results may be interchangeable. The average duration of follow-up is short and longer-term follow-up is needed. However, the recently reported long-term data demonstrated that the IVUS findings in the FIM trial at 4 months remained essentially unchanged at 12 months[11] and up to 2 years[36] supporting the notion that early findings may be predictive of the findings at long-term follow-up.

Conclusion

Sirolimus-eluting stents appear to be as effective at inhibiting neointimal hyperplasia in ISR lesion as it is in de novo lesions without inducing edge effect or positive vascular remodelling.

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