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Clinical research

Therapeutic implications of in-stent restenosis located at the stent edge.

Insights from the Restenosis Intra-stent Balloon angioplasty versus elective Stenting (RIBS) randomized trial

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Aims In patients with in-stent restenosis (ISR) several anatomic subgroups have been identified. ISR affecting the stent edge (EDG) is a poorly characterised subgroup with undefined therapeutic implications. We sought to determine the implications of ISR affecting the stent EDG.

Methods and results 450 patients included in the ''Restenosis Intra-stent: Balloon angioplasty vs elective Stenting'' (RIBS) randomized study, were analysed. EDG ISR was predefined in the protocol and the pattern of ISR analysed in a centralized core-lab. Fifty-two patients (12%) had EDG ISR (29 stent group, 23 balloon arm). Patients with EDG ISR had less severe [minimal lumen diameter (MLD) (0.78 ± 0.3 vs 0.66 ± 0.3 mm, $p = 0.05$)] and shorter lesions (lesion length 10.2 ± 6 vs 13.2 ± 7 mm, $p = 0.003$). Patients with EDG ISR more frequently required crossover (12% vs

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3%, $p = 0.006$) but eventually the immediate angiographic result and the long-term clinical and angiographic outcome was similar to that found in patients without EDG ISR. Patients with EDG ISR treated in the balloon and stent arms had similar baseline characteristics. However, after intervention, the immediate angiographic result was better in the stent arm (MLD 2.79 ± 0.4 vs 2.35 ± 0.3 mm, $p = 0.001$). This difference persisted at late follow-up: MLD (1.93 ± 0.7 vs 1.39 ± 0.7 mm, $p = 0.01$), recurrent restenosis (20% vs 50%, $p = 0.03$). In addition, the 1-year event-free survival was significantly better (83% vs 52%, log rank $p = 0.01$; Cox HR 0.28, 95%CI 0.09—0.79) in the stent arm. Moreover, stent implantation was an independent predictor of freedom from target vessel revascularization (HR 0.15, 95%CI 0.03—0.67, $p = 0.003$).

Conclusions EDG ISR constitutes a specific subgroup with relevant therapeutic implications. In patients with EDG ISR, repeat stent implantation provides better clinical and angiographic outcome than conventional balloon angioplasty.

Introduction

Management of patients with in-stent restenosis (ISR) constitutes a technical challenge.[1—15] Different mechanical alternatives have been suggested in this setting,[11—15] but so far, no mechanical device has been able to significantly improve the long-term outcome. The effectiveness of brachytherapy in these patients is well-established but this technique has inherent problems and limitations and it is not widely available.[16—18] There is still a need therefore to determine which mechanical intervention is best suited for specific cohorts of patients with ISR.

In this study, we investigated the implications of a specific angiographic pattern of ISR, namely ''edge'' ISR. Patients with edge ISR represent an interesting subset because they have the narrowing located at the stent margin extending to some extent to the adjacent unstented vessel, while most of the stent length remains free of significant disease. This pattern of ISR was predefined and prospectively analysed in the Restenosis Intra-stent Balloon angioplasty versus elective Stenting (RIBS) randomized study.[19] In RIBS both strategies yielded similar long-tem clinical and angiographic results except for patients with large vessels ($\geqslant$ 3 mm) who did significantly better after repeat stenting. In this report we compared the baseline characteristics of patients with edge ISR with the remaining patients included in the RIBS trial. In addition, we examined if this angiographic pattern conveyed prognostic or therapeutic implications.

Methods

Patient selection, procedures and protocol

The inclusion criteria, design and primary end-points of the RIBS trial have been previously reported.[19] Briefly, patients with a first ISR with either angina or evidence of ischaemia were eligible if they had lesions amenable to both interventional strategies. The target lesion had to be shorter than 32 mm in length and located in a vessel >2.5 mm in diameter. Lesion predilatation (conventional balloon) was required before repeated stenting but debulking devices were not used in the study. Written informed consent was obtained from all patients.

During coronary interventions, balloon size was selected to ensure a balloon-to-artery ratio of 1.1/1 and relatively high pressures (>12 atm) were recommended in both arms (final pressure for patients randomized to repeat stenting 13.5 ± 2 atm). In patients allocated to repeat stenting a non-coil stent design was always selected.[19] Treatment of the target lesion was performed focusing on the narrowing, this was independent of whether this also implied dilation of the coronary segment immediately adjacent to the site of the initial stent. This occurred mainly in patients with proliferative and ''edge'' patterns of ISR. Alternatively, in patients with underlying long stents, but housing just a relatively focal narrowing, only the lesion site was treated. Cross-over to the other arm was discouraged in the protocol and prolonged balloon inflations had to be attempted before cross-over to stent deployment.[19]

After the procedure all patients received aspirin whereas patients treated with repeated stenting also received ticlopidine for one month. Patients were followed-up at 1, 6 and 7 months and at 1 year. Angiographic follow-up was obtained routinely at 6-months or earlier if clinically indicated. Case report forms were forwarded to the co-ordinating centre where data were verified (consistency checks) and codified. Clinical events (death, myocardial infarction target vessel revascularization) were adjudicated by an independent Clinical Events Committee blinded to the assigned treatment. Clinical follow-up at 1-year was obtained in all 450 patients (100%) included in the trial.

Angiographic analysis

All cine films and CDs were analysed at the angiographic core laboratory by experienced personnel blinded to treatment allocation.[19] Special care was taken in trying to identify the site of initial stent deployment and the relative geographic position of the narrowing. Detailed drawings of these two sites and of the treated segment were systematically reviewed. By the protocol, all patients had restenosis ''within'' the stent. Patients were divided into two groups: with or without edge ISR, according to a classification scheme also provided on the case report forms. Edge ISR required that $\geqslant$ 3 mm (absolute) or 25%

(relative) of the lesion length had to be located ''within'' the stent but most of the stent length remained free from significant disease. Thus, the lesion extended for a variable extent into the adjacent unscaffolded vessel. In 3 patients with edge ISR, intravascular ultrasound was required to ensure that the narrowing was indeed located within the stent. Therefore, this classification differs in part from the previous classification of Mehran et al.,[15] (published after the current trial was initiated) where ''margin'' ISR (Type I B), was only reserved for patients with ''focal'' ($\leqslant$10 mm) patterns of in-stent restenosis. The presence of edge ISR was subsequently evaluated at the angiographic core lab. Queries were sent back to the clinical sites in the event of disagreement and, eventually, a decision was taken at the core lab.

Quantitative coronary angiographic analysis was performed with an automatic edge-detection algorithm (MEDIS, CMS 4.0, Leiden, the Netherlands). Matched angiographic views were analysed before, after intervention and at follow-up.[20,21] Restenosis was defined as >50% diameter stenosis at follow-up. Quantitative angiographic data at follow-up was available in 415 patients (95% of those eligible).

Statistical analysis

Data are presented as absolute values and percentages or means ± SD. Categorical variables were compared with the chi-square test or Fisher's exact test. For the comparison of continuous variables a two-tailed Student *t*-test or Wilcoxon rank-sum test were used. Event-free survival was estimated with Kaplan—Meier analysis and compared with the log-rank test. Cox proportional hazard analyses were used to determine independent predictors of events in patients with edge ISR. Variables with a *p*-value <0.1 in the univariate analysis were included in the multivariate analysis. Proportional hazards assumptions were evaluated with the Goodness-of-Fit testing approach. All analyses were performed according to the intention-to-treat principle, using the SPSS package (version 10.0). All statistical tests were two-sided. A *p*-value <0.05 was considered statistically significant.

Results

Of the 450 patients enrolled in the trial (224 stent arm, 226 balloon arm), 52 (12%) had ISR located at the stent edge. Table 1 compares the baseline characteristics of these patients with those of the remaining 398 patients without edge ISR. The two groups were quite similar but patients with edge ISR were less frequently smokers and had a lower incidence of hypertension. The underlying initial stent had a non-coil design in 9 patients with edge ISR (17%) and in 54 with ISR not located at the edge (13%), ($p = 0.46$). No particular stent design

Table 1 Baseline clinical, angiographic and procedural characteristics

Characteristic	EDG ISR (*N* = 52)	No EDG ISR (*N* = 398)	*p*-value
Age (y)	61 ± 11	59 ± 10	0.18
Female sex — No. (%)	11 (21)	90 (23)	0.81
Risk Factors — No. (%)			
— Diabetes mellitus	10 (19)	107 (27)	0.24
— Hyperlipidaemia	32 (61)	217 (55)	0.38
— Hypertension	21 (40)	226 (57)	0.02
— Ever smoked	23 (44)	235 (59)	0.04
Clinical features — No. (%)			
— Unstable angina	21 (40)	171 (43)	0.72
— Stable angina	24 (46)	202 (51)	0.53
— Silent ischaemia	7 (14)	25 (6)	0.08
— Previous myocardial infarction	19 (37)	174 (44)	0.33
— Previous bypass surgery	2 (4)	17 (4)	1
Time to restenosis[a] (days)	240 ± 198	209 ± 143	0.20
Target artery — No. (%)			0.49
— Left anterior descending	30 (58)	205 (52)	
— Left circumflex	10 (19)	78 (20)	
— Right coronary	10 (19)	108 (27)	
— Saphenous vein graft	2 (4)	7 (2)	
B2-C lesion	35 (69)	312 (80)	0.07
Ejection fraction (%)	65 ± 12	64 ± 11	0.56
Procedural characteristics			
— Length of initial Stent (mm)	19 ± 8	19 ± 8	0.8
— Maximal pressure (atm)	12.9 ± 3	13.0 ± 3	0.66
— Total inflation time (s)	117 ± 95	157 ± 107	0.01
— Balloon/artery ratio	1.10 ± 0.1	1.11 ± 0.2	0.69
— Cross-over	6 (12)	10 (3)	0.006
— Angiographic success	51 (98)	397 (99)	0.22

[a] Elapsed time from initial stent implantation to the repeated procedure.

was associated with a higher likelihood of edge ISR. However, lesions with edge ISR were shorter, less severe, and tended to have a less complex morphology (Tables 1 and 2). Although some patients with edge ISR had long lesions, a diffuse (>10 mm) pattern was less frequently found in patients with edge ISR. By protocol, all patients allocated to repeat stenting required balloon pre-dilatation. However, eventually 14 patients (4 with and 10 without edge ISR) eventually underwent direct stenting. After the procedure, angiographic results were similar in both groups (Table 2) although cross-over was more frequently required in patients with edge ISR. In addition, both groups had similar angiographic results at late (median 188 days) angiographic analysis (Table 2). Finally, the event free survival was similar in patients with and without edge ISR (69% vs 75%, log rank $p = 0.46$). Table 3 summarizes events at 1 year in both groups.

Of the 52 patients with edge ISR, 29 were allocated to the stent arm and 23 to the balloon arm. All baseline clinical and angiographic characteristics were well matched in these two groups (Table 4). During the procedure the inflation time was shorter and residual dissections were less frequent in the stent group [2 (8%) vs 8 (36%), $p = 0.03$]. On quantitative coronary angiography better angiographic results were obtained in the stent group (Table 5). At follow-up patients with edge ISR allocated to repeat stenting maintained better angiographic results including minimal lumen diameter, percent diameter stenosis and net gain. Recurrent restenosis only occurred in 5 patients in the stent group (20%) versus 11 (50%) of patients in the balloon arm (RR 0.4, 95%CI: 0.16—0.97, $p = 0.03$). In addition, the event-free survival (Fig. 1) was significantly better in the stent group (HR 0.28, 95%CI: 0.09—0.79, Cox $p = 0.012$). This was the consequence of a lower requirement for target vessel revascularization during follow-up [3 (10%) vs 10 (44%), HR 0.2, 95%CI: 0.05—0.72, Cox $p = 0.006$], mainly as the result of fewer repeated percutaneous coronary interventions [1 (3%) vs 6 (26%), HR 0.12, 95%CI: 0.01—0.99, Cox $p = 0.016$].

In patients with edge ISR, the baseline minimal lumen diameter, lesion length and stent allocation were associated (univariate analysis) with clinical outcome. However, upon Cox multivariate analysis, only stent therapy (HR 0.29, 95%CI 0.09—0.96, $p = 0.03$) and minimal lumen diameter before intervention (HR 0.22, 95%CI 0.05—1.09, $p = 0.06$) were identified as independent predictors of the absence of clinical events at follow-up. In addition, in these patients, the time to ISR, ostial location, B2C morphology, ISR length, baseline minimal lumen diameter and stent therapy were univariate predictors of target vessel revascularization at follow-up. However, stent implantation was the only independent predictor of freedom from target vessel revascularization (HR 0.15, 95%CI 0.03—0.67, $p = 0.003$).

Discussion

This study demonstrates that patients with ''edge'' ISR represent a small but unique subgroup with differentiated baseline characteristics and important therapeutic implications. In our series, patients with edge ISR had a relatively benign clinical and angiographic profile as compared with other patients with ISR. However, overall, they had a high recurrent restenosis rate and also a high need for target vessel revascularization. The present study demonstrates that the use of stents in these patients significantly reduces the rate of recurrent restenosis and target vessel revascularization. In fact, after correction for other confounding factors stent treatment

Table 2 Quantitative angiographic findings

Variable	EDG ISR	No EDG ISR	*p*-value
Before the procedure	(*N* = 52)	(*N* = 398)	
Reference vessel diameter (mm)	2.87 ± 0.4	2.85 ± 0.5	0.81
Minimal lumen diameter (mm)	0.78 ± 0.3	0.66 ± 0.3	0.05
Stenosis (% of lumen diameter)	73 ± 12	77 ± 12	0.06
Lesion length (mm)	10.2 ± 6	13.2 ± 7	0.003
Diffuse lesions (>10 mm) — No. (%)	19 (38)	243 (62)	0.001
After the procedure	(*N* = 52)	(*N* = 398)	
Reference vessel diameter (mm)	3.04 ± 0.4	3.02 ± 0.5	0.58
Minimal lumen diameter (mm)	2.59 ± 0.4	2.50 ± 0.5	0.29
Stenosis (% of lumen diameter)	17 ± 16	17 ± 11	0.85
Acute gain (mm)	1.81 ± 0.5	1.84 ± 0.6	0.80
At Follow-up: (''per segment'' analysis)	(*N* = 47)	(*N* = 368)	
Reference vessel diameter (mm)	2.89 ± 0.4	2.86 ± 0.5	0.68
Minimal lumen diameter (mm)	1.68 ± 0.8	1.56 ± 0.8	0.35
Stenosis (% of lumen diameter)	41 ± 24	46 ± 24	0.21
Restenosis — No. (%)	16 (34)	145 (39)	0.48
Late loss (mm)	0.91 ± 0.7	0.93 ± 0.8	0.86
Loss index	0.48 ± 0.3	0.49 ± 0.4	0.98
Net gain (mm)	0.91 ± 0.6	0.90 ± 0.8	0.97

Table 3 Clinical events at 1-year

Event	EDG ISR (52)		No EDG ISR (398)		*p*-value	Hazard ratio (95% CI)
	N (%)	% EFS	*N* (%)	% EFS		
Death	1 (2%)	98 ± 19	14 (4%)	96 ± 1	0.54	0.55 (0.07–4.07)
Myocardial infarction	3 (6%)	94 ± 3	16 (4%)	96 ± 1	0.97	1.43 (0.43–4.76)
Death or myocardial infarction	4 (8%)	92 ± 4	25 (6%)	94 ± 1	0.95	1.22 (0.44–3.38)
TVR	13 (25%)	75 ± 6	86 (22%)	78 ± 2	0.65	1.16 (0.70–1.92)
— Coronary angioplasty	7 (14%)	87 ± 5	68 (17%)	83 ± 2	0.44	0.79 (0.38–1.62)
— Coronary surgery	6 (12%)	88 ± 4	21 (5%)	95 ± 1	0.07	2.19 (0.92–5.17)
Any major event at 1 year[a]	16 (31%)	69 ± 6	101 (25%)	75 ± 2	0.61	1.21 (0.78–1.88)

% EFS: cumulative event-free survival. CI denotes confidence intervals. TVR = target vessel revascularization. (*p*-values from Cox analysis).
[a] Patients with more than one event are counted only once for the composite clinical endpoints although each event is listed separately in the corresponding category.

Table 4 Baseline characteristics of patients with edge in-stent restenosis according to treatment allocation

Characteristic	Stent (*N* = 29)	Balloon (*N* = 23)	*p*-value
Age (y)	58 ± 10	60 ± 11	0.63
Female sex — No. (%)	8 (28)	3 (13)	0.31
Risk factors — No. (%)			
— Diabetes mellitus	7 (24)	3 (13)	0.48
— Hyperlipidaemia	20 (69)	12 (52)	0.22
— Hypertension	13 (45)	8 (35)	0.46
— Ever smoked	11 (38)	12 (52)	0.30
Clinical features — No. (%)			
— Unstable angina	12 (41)	9 (39)	0.87
— Stable angina	12 (41)	12 (52)	0.44
— Silent ischaemia	5 (17)	2 (9)	0.44
— Previous myocardial infarction	12 (41)	7 (30)	0.42
— Previous bypass surgery	1 (3)	1 (4)	1
Time to restenosis:[a] days	269 ± 197	204 ± 183	0.23
Target artery — No. (%)			0.44
— Left anterior descending	14 (49)	16 (70)	
— Left circumflex	7 (24)	3 (13)	
— Right coronary	7 (24)	3 (13)	
— Saphenous vein graft	1 (3)	1 (4)	
B2-C lesion	17 (61)	18 (78)	0.18
Ejection fraction (%)	65 ± 12	63 ± 10	0.41
Procedural characteristics			
— Maximal pressure (atm)	12.9 ± 2	12.9 ± 4	0.95
— Total inflation time (s)	89 ± 52	152 ± 123	0.03
— Balloon/artery ratio	1.09 ± 0.2	1.12 ± 0.1	0.38
— Cross-over	1 (3)	5 (22)	0.08
— Angiographic success	28 (97)	23 (100)	1

[a] Elapsed time from initial stent implantation to the repeated procedure.

emerged as an independent predictor of a favourable clinical outcome. The potential additional benefit of drug-eluting stents in patients with edge ISR warrants prospective evaluation.

No previous study has analysed this important subset of patients in detail. In the study of Mehran et al.,[15] all patients with edge ISR had ''focal'' (type I) ISR and, therefore, constitute a slightly different patient population. Additionally in that study, although the overall clinical outcome of patients with ''focal'' ISR was favourable, no data was provided concerning patients with the specific pattern of margin (Type I B) ISR. Our findings suggest that although most edge ISR are relatively focal some of these lesions may present a diffuse pattern.

A unique characteristic of patients with edge ISR is that they present the narrowing relatively localized at the stent margin, with most of the remaining stent length free of significant disease. Another major characteristic of this subgroup is that in most patients the lesion is also affecting the adjacent unscaffolded vessel for a variable length.[15] Therefore, these patients share characteristics of ISR lesions and also of classic

Table 5 Quantitative coronary angiography findings of patients with edge in-stent restenosis according to treatment allocation

Variable	Stent	Balloon	*p*-value
Before the procedure	(*N* = 27)	(*N* = 23)	
Reference vessel diameter (mm)	2.91 ± 0.4	2.82 ± 0.4	0.44
Minimal lumen diameter (mm)	0.84 ± 0.4	0.70 ± 0.3	0.17
Stenosis (% of lumen diameter)	72 ± 12	75 ± 11	0.33
Lesion length (mm)	8.9 ± 5	11.7 ± 7	0.10
Diffuse lesions (>10 mm) — No. (%)	8 (30)	11 (48)	0.25
After the procedure	(*N* = 27)	(*N* = 23)	
Reference vessel diameter (mm)	3.12 ± 0.4	2.97 ± 0.3	0.20
Minimal lumen diameter (mm)	2.79 ± 0.4	2.35 ± 0.3	0.001
Stenosis (% of lumen diameter)	14 ± 19	20 ± 9	0.13
Acute gain (mm)	1.95 ± 0.5	1.66 ± 0.5	0.05
At follow-up: (''per segment'' analysis)	(*N* = 25)	(*N* = 22)	
Reference vessel diameter (mm)	2.94 ± 0.4	2.84 ± 0.3	0.36
Minimal lumen diameter (mm)	1.93 ± 0.7	1.39 ± 0.7	0.01
Stenosis (% of lumen diameter)	33 ± 19	51 ± 25	0.008
Restenosis — No. (%)	5 (20)	11 (50)	0.03
Late loss (mm)	0.81 ± 0.6	1.01 ± 0.8	0.36
Loss Index	0.42 ± 0.3	0.55 ± 0.4	0.21
Net gain (mm)	1.12 ± 0.6	0.66 ± 0.6	0.02

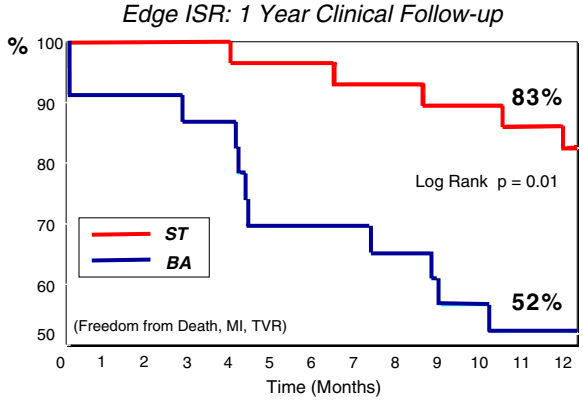

Fig. 1 Kaplan–Meier estimates of event-free survival of patients with edge in-stent restenosis (ISR) according to treatment allocation. ST = Stent. BA = Balloon angioplasty (1-year follow-up: ST 83 ± 7%, BA 52 ± 10%).

restenotic lesions after balloon angioplasty. It is well-established that the underlying pathophysiological mechanism of these two lesion subsets is largely different. In patients with ISR, stent recoil is absent or negligible and late lumen loss is almost exclusively the result of neointimal tissue within the stent.[22–23] Conversely, in patients showing restenosis in non-stented vessels, negative vessel remodelling appears to be the most relevant factor accounting for the appearance of restenosis.[24]

From our findings, it is attractive to speculate that the best results obtained by repeat stenting in patients with edge in-stent restenois may be due, at least in part, to the fact that a significant proportion of the restenosis being treated was outside the stent. In this regard it is important to keep in mind the results of the REST randomized trial, where stents proved to be superior to balloon angioplasty in patients with not previously stented restenotic lesions.[25] In these lesions the scaffolding properties of stents are able to provide a better clinical and angiographic outcome. The better initial results obtained by stent implantation in this setting largely outweighs the greater (more than two-fold) late loss at follow-up, eventually resulting in larger net gain and minimal lumen diameter at follow-up.[25]

Limitations

First, the present study only includes a relatively small number of patients with edge ISR. Nevertheless, this specific angiographic pattern was prospectively assessed in our large series of patients and subsequently analysed in a centralized core-lab. In addition, the benefit of repeat stenting was not just an angiographic finding but also correlated with clinical benefit and persisted after adjustment for potential confounders. Second, only intravascular ultrasound may accurately depict the geographic position of the intimal hyperplasia (extent and length) obstructing the previously implanted stent.[22–24]

Conclusions

Patients with edge ISR represent a relatively small but unique subgroup of patients, with major therapeutic implications, thus allowing an early triage. Our findings suggest that, in these patients, repeat stenting provides better long-term clinical and angiographic results than conventional balloon angioplasty and, therefore, should be recommended.

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