# *Clinical variables related with in-stent restenosis late regression after bare metal coronary stenting*

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## Summary

In-stent restenosis (ISR) has an incidence between 20% and 30% using bare metal stents. ISR late regression phenomenon (ISRLR) has been previously described, but clinical variables related with this phenomenon remain unclear. The aim of the study was to identify the variables related with ISRLR. **Methods:** We identified from our data base 30 patients between November 1995 and September 2002 that fulfilled the following criteria: 1) Documented ISR at follow-up angiography (CA-1); 2) treated medically; and 3) Referred for a second follow-up angiography (CA-2) at least 3 months after CA-1. ISRLR was defined as a > 0.2 mm increase in MLD between CA-1 and CA-2, calculated as the 2-fold of our inter-observer variability. ISR late progression was defined as a > 0.2 mm decrease in minimum lumen diameter (MLD) between CA-1 and CA-2. **Results:** At the time of CA-2 only 2 patients (6.7%) had symptoms related with the previously stented vessel. We found a mean MLD of 1.03 ± 0.34 mm and 1.54 ± 0.48 mm at CA-1 and CA-2 respectively (ΔMLD = 0.51 ± 0.34 mm; p < 0.001). Twenty four patients (80.0%) had ISRLR. Two variables were related to the presence or absence ISRLR: Current smoking at the time of coronary stenting (70.8% *vs* 20.0% respectively, p = 0.026) and acute coronary syndrome as clinical indication for coronary stenting (and 83.5% *vs* 40.0% respectively, p = 0.029). **Conclusion:** ISRLR is a frequent phenomenon in patients with ISR treated medically, probably contributing to the benign long-term clinical outcome that has been previously described in patients with asymptomatic or mildly symptomatic ISR. Current smoking at the time of

## Resumen

REGRESIÓN TARDÍA DE LA ESTENOSIS INTRASTENT

La reestenosis intrastent (RIS) tiene una incidencia del 20 al 30% cuando se utilizan stents convencionales. El fenómeno de regresión tardía de (RTRIS) ha sido descrito previamente, pero no se han identificado variables relacionadas con dicho fenómeno. El objetivo del estudio fue identificar variables relacionadas con la RTRIS. **Métodos:** Identificamos en nuestra base de datos 30 pacientes con los siguientes criterios: 1) RIS identificada durante el seguimiento angiográfico (AC-1); 2) sujetos que permanecieron con tratamiento médico; 3) referidos para una angiografía de seguimiento (AC-2) al menos 3 meses posteriores a la AC-1. RTRIS fue definida como un incremento del diámetro luminal mínimo (DLM) > 0.2 mm entre la AC-1 y AC-2, calculado a partir del doble del valor de nuestra variabilidad interobservador. La progresión tardía de la RIS, se definió como un decremento en el DLM > 0.2 mm entre AC-1 y AC-2. **Resultados:** Al momento de la AC-2 sólo 2 pacientes (6.7%) tenían síntomas relacionados con el vaso blanco del tratamiento. Encontramos una media de DLM de 1.03 ± 0.34 mm y 1.54 ± 0.48 mm en AC-1 y AC-2 respectivamente (p < 0.001; ΔDLM = 0.51 ± 0.34 mm). Del total de 30 pacientes, 24 (80.0%) tenían RTRIS. Existieron dos variables relacionadas con la presencia o ausencia de RTRIS: Fumar concordantemente con el tiempo de la implantación del stent (70.8% *vs* 20.0% respectivamente, p = 0.026) y la existencia de un síndrome coronario agudo (SICA) como indicación para el tratamiento inicial (83.5% *vs* 40.0% respectivamente, p = 0.029).

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coronary stenting and acute coronary syndrome as clinical indication for coronary stenting are associated with this phenomenon.

**Conclusión:** La RTRIS es un fenómeno frecuente en pacientes con RIS que permanecen con tratamiento médico, hecho que probablemente contribuye con la evolución clínica benigna que ha sido previamente descrita, en pacientes con RIS asintomáticos o con escasa sintomatología. Sujetos fumadores al momento de la implantación del stent así como SICA como indicación al tratamiento inicial, son situaciones asociadas con la presentación de RTRIS.
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**Key words:** Coronary stenting. In-stent restenosis. Late regression.
**Palabras clave:** Stent convencional. Reestenosis intra-stent. Regresión tardía.

## Introduction

In-stent restenosis (ISR) is still the Achilles heel of the coronary intervention, with an estimated incidence between 20% and 30% of the procedures using bare metal stents (BMS);[1,2] mainly within 3 to 6 months after the stent implantation.[3,4] ISR late regression (ISRLR) is a previously described phenomenon.[5,6] The mechanisms involved, however, are not fully understood. Kimura et al[7] demonstrated a late improvement in the luminal diameter after Palmaz-Schatz coronary stenting, with an increase in minimum lumen diameter after 6 months and 3 years following stent implantation. Hermiller et al[8] also observed ISR regression after 3 years using Gianturco Roubin stents. More recently Miereles et al,[9] demonstrated that using thick strut stent in de novo lesions, resulted in significantly increased MLD from 6 to 12 months; and also observed that binary restenosis were reduced from 17% at 6 *vs* 11% at 12 months although non statistically significant. In contrary Sadamatsu K et al.[10] demonstrated that older age, diabetes mellitus, hyperlipidemia, smoking and small stent diameter (< 3.0 mm) were associated with late luminal loss beyond 6 months after implantation of thicker strut stents.

Although we are in era of drug eluting stents[11] and intracoronary brachytherapy,[12] there are still many patients treated with BMS with ISR, and thus knowledge about factors influencing ISRLR remains an issue of clinical relevance.

The aim of this study was to elucidate which clinical and angiographic variables are related with ISRLR.

## Methods

### Study population

Out of 1,001 patients with angiographically documented ISR (stenosis severity ≥ 50%) at follow-up angiography (CA-1: 6.0 ± 2.3 months after stent implantation), we selected from our data base 30 cases that fulfilled the following two additional inclusion criteria: 1) Treated medically; 2) Referred for a second follow-up angiography > 3 months after CA-1 (CA-2: 24.8 ± 21.6 months after stent implantation). *Figure 1* shows the flow-chat for the selection of the patients.

### Stenting procedure[13]

Cardiac catheterization was performed by femoral approach in most patients. All of them were pre-treated with aspirin, and heparin was administered as an intra-coronary bolus at the beginning of the procedure, and additional boluses were given when necessary to maintain an activated clotting time > 300 seconds (200-250 seconds when IIb/IIIa inhibitors were administered). Provisional or direct stenting was performed at the discretion of the operator, and balloon-to-artery ratio was 1.0-1.1/1.

### Coronary angiography analysis

Quantitative coronary angiographic analysis was performed using a validated, automatic edge-detection algorithm (MEDIS, CMS 4.0, Leiden, the Netherlands).[14] Similar angiographic views demonstrating maximal stenosis were reviewed for the same vessel segment in CA1 and CA2 studies. The minimal lumen diameter (MLD) was defined angiographically as the minimal vessel diameter within the stent. ΔMLD was defined as the differ-

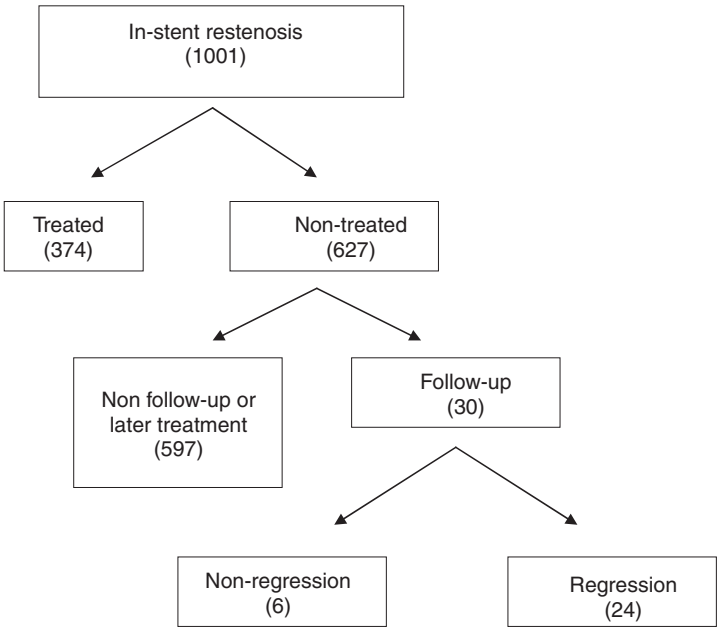


**Fig. 1.** Selection of study patients.

**Table I.** Demographic and clinical characteristics of 30 study patients.

| | |
|---|---|
| Mean age (years) | 61.5 ± 11.15 |
| Male | 22 (73.3%) |
| Coronary risk factors | |
| Hypertension | 22 (73.3%) |
| Diabetes mellitus | 11 (36.6%) |
| Smoking | 18 (60%) |
| Hypercholesterolemia | 22 (73.3%) |
| Previous AMI | 13 (43.3%) |
| ACS during coronary stenting | 22 (73.3%) |
| Target Vessel | |
| Left main | 1 (3.3%) |
| LAD | 17 (56.6%) |
| LCX | 5 (16.6%) |
| RCA | 7 (23.3%) |
| ISR type[31] I | 12 (40%) |
| ISR type II | 18 (60%) |
| Early ISR (< 3 months) | 3 (10%) |

LAD: Left anterior descending. LCX: Left circumflex. RCA: Right coronary artery. ACS: Acute coronary syndrome. AMI: Acute myocardial infarction. ISR: In-stent restenosis.

ence between MLD at CA2 and CA1. ΔSP was calculated as the difference between in-stent stenosis percentage (SP) at CA-2 and CA-1.

Two different, technically trained investigators analyzed the 2 angiograms of each individual patient, blinded to the order of follow-up cine-angiograms (CA-1 or CA-2). The inter-observer variability was 0.1 ± 0.11 mm and 4.23 ± 4.27% in measuring MLD and SP respectively. ISRLR was defined as a > 0.2 mm increase in MLD between CA-1 and CA-2, which was calculated as the 2-fold of the inter-observer variability. ISR late progression was defined as a > 0.2 mm decrease in MLD between CA-1 and CA-2.

### Statistical analysis

Statistical analysis was performed using the SPSS package, version 10.0 (*Chicago, Illinois, USA*). Continuous variables were presented as mean ± standard deviation, and discrete variables as proportions (percentages). Student's t, Pearson's chi-square, and Fisher's exact test were performed as indicated. A p value < 0.05 was considered statistically significant.

## Results

### Baseline clinical and angiographic characteristics

Baseline characteristics are presented in *Table I*. Mean age was 61.5 ± 11.2 years, and 73.3% of patients were male gender. The indication for coronary stenting was acute coronary syndrome in 22 (73.3%), and chronic ischaemic heart disease in 8 (26.7%) patients. Only 3 patients (10%) had an early (< 3 months since stent implantation) ISR.

Elective, bailout and direct stenting was performed in 21 (70.0%), 6 (20.0%), and 3 (10.0%) patients, respectively. Mean stent diameter was 3.1 ± 0.5 mm and mean stent length was 21.2 ± 8.8 mm. Relatively high pressures were used (12.6 ± 3.1 atm). The type of stent was Multi-Link in 7 (23.3%), NIR in 7 (23.3%), Velocity in 6 (20.0%), and other types in 10 (33.3%) patients, therefore the great majority of stents used were thick strut devices (≥ 100 $\mu$m: Multi-Link, NIR and Velocity).

At the time of CA-1, 11 patients (36.7%) were symptomatic, and 19 (63.3%) asymptomatic. At the time of CA-2, most patients (n = 28; 93.3%) were symptomatic, although only in 2 cases symptoms were related with the previously stented segment: one of them had unstable angina due to ISR late progression and was referred for coronary artery bypass grafting, and the other had stable angina and was treated medically.

### Long-term angiographic outcome

Mean time from CA-1 to CA-2 was 18.7 ± 20.8 months (range 3.2-113.4). Mean MLD was 1.03 ± 0.34 mm and 1.54 ± 0.48 mm at CA-1 and CA-2, respectively ($p < 0.001$; ΔMLD = 0.51 ± 0.34 mm). Mean Stenosis percentage was 59.1 ± 5.8% and 37.7 ± 16.0% at CA-1 and CA-2, respectively ($p < 0.001$; ΔSP = 21.4 ± 15.5%). Mean reference vessel diameter did not vary significantly between CA-1 and CA-2 (2.6 ± 0.8, and 2.5 ± 0.7 mm respectively, p = 0.49). Twenty-four patients (80.0%) had ISRLR, whereas ISR late progression occurred in one patient (3.3%). In the remaining 5 patients (16.7%), there was neither ISRLR nor ISR late progression. At CA-2, only 4 patients (13.3%) had > 50% SP. The individual ΔMLD are displayed in *Figure 2*.

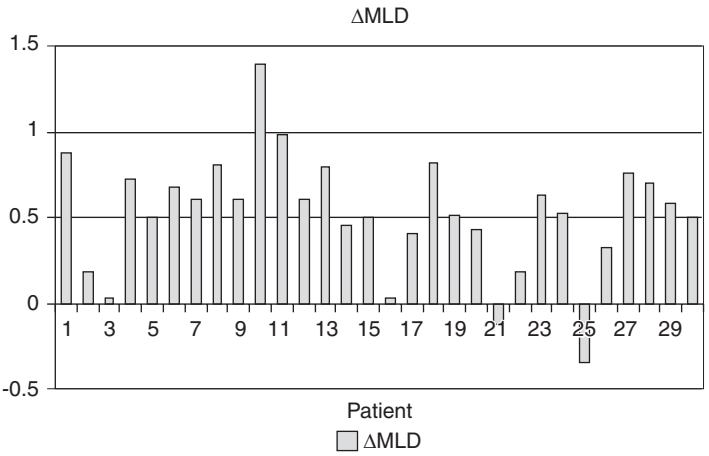


**Fig. 2.** Individual ΔMLD.

### Characteristics associated with ISRLR *(Table II)*

For patients with ISRLR, smoking at the time of stent implantation is related to ISRLR (70.8% *vs* 20.0%, p = 0.026).

Acute coronary syndrome as indication for coronary stenting was also related with ISRLR (83.5% *vs* 40.0%, p = 0.029).

## Discussion

### Late regression of ISR.

ISRLR is a well-documented phenomenon, although there is still debate whether it is a constant or a random finding in the evolution of ISR. The underlying mechanisms of ISRLR are not clear. According to the study by Asakura et al,[15] neointimal thickening and subsequent thinning may be the main responsible mechanisms. Other groups have proposed the absence of continuous vascular injury during the time (which initially explains the relatively early hyperplastic response after the stent delivery), as the mechanism of neointima late remodelling.[5] Kimura et

**Table II.** Covariate analysis.

| Variable | ISRLR | No. ISRLR | p value |
|---|---|---|---|
| Male | 17 (70.8%) | 5 (20.8%) | |
| Smoking at the time of stenting | 17 (70.8%) | 1 (4.1%) | 0.026 |
| Hypertension | 17 (70.8%) | 5 (20.8%) | |
| Hypercholesterolemia | 18 (75%) | 4 (16.6%) | |
| Diabetes mellitus | 8 (33.3%) | 3 (12.5%) | |
| Target Vessel | | | |
| Left main | 1 (4.1%) | 0 (0%) | |
| Left anterior descending | 14 (58.3%) | 3 (12.5%) | |
| Left circumflex | 4 (16.6%) | 1 ( 4.1%) | |
| Right coronary artery | 5 (20.8%) | 2 (8.3%) | |
| Acute coronary syndrome at stenting | 20 (83.3%) | 2 (8.3%) | 0.029 |
| Indication for stenting | | | |
| Elective | 18 (75%) | 3 (12.5%) | |
| Bail-out | 4 (16.6%) | 2 (8.3%) | |
| Direct | 3 (12.5%) | 0 (0%) | |
| Lesion type | | | |
| A | 6 (25%) | 0 (0%) | |
| B2-C | 18 (75%) | 5 (20.8%) | |

NS: Non-significant. ISRLR: In-stent restenosis late regression.

al[16] demonstrated late improvement in the luminal diameter in patients who received Palmaz-Schatz stents. They found that MLD was significantly larger at 3 years in comparison with that after 6 months of stent implantation, and proposed a mechanism of fibrotic maturation of intimal hyperplasia similar to wound healing.

Our results show that ISRLR may occur in a high proportion of patients with ISR that are treated conservatively. In our study, ISRLR was documented in 80% of patients, and 86.6% of patients had a < 50% SP at long-term follow-up. This proportion is high, although not out of the range found in previous studies: Mehta et al[5] reported an ISRLR of 78% in their study population. However, due to the selection criteria, patients with ISR that comprised our study population, as also occurred in other similar studies, are within the range of less severe ISR (~60% by quantitative coronary analysis) and more benign clinical situation. In patients with more severe ISR the proportion of patients with ISRLR could be lower.

Current smoking at the time of coronary stenting was significantly associated with higher frequency of ISRLR. Historically, controversy has existed regarding the relation of smoking and ISR, since Arora et al[17] found non-significantly lower restenosis rates in patients who smoked at the time of percutaneous coronary intervention. Melkerk et al[18] showed that a history of cigarette smoking was a protective factor of restenosis at six months. Kotakami et al[19] also observed a lower restenosis rate in current smokers, although they were younger and had less severe lesions than non-smokers. On the contrary, Galan et al[20] found higher restenosis rates in patients who continued smoking in comparison with that in those who ceased smoking. Finally, Violaris et al[21] found no significant differences in the rate of ISR at 6 months among current smokers, ex-smokers and non-smokers. We have not found any previous study relating smoking with ISRLR.

Another relevant finding of our study was the higher frequency of ISRLR among patients that presented with an acute coronary syndrome at the time of coronary stenting. Several studies have demonstrated high rates of restenosis in patients with unstable ischemic heart disease.[22-24] In fact we found a high percentage (73%) of patients with acute coronary syndrome at the time of coronary stenting in our population of patients with ISR. To the best of our knowledge, there is no previously published information showing an association between ISRLR and the clinical situation at the time of coronary stenting. A retarded apoptosis phenomena could be involved.[25,26]

## Conclusion

There seems to exist consensus about the benign prognosis of asymptomatic restenosis, both after balloon angioplasty[27,28] and after coronary stent implantation.[29,30] The phenomenon of ISRLR probably contributes to the benign long-term clinical outcome of asymptomatic patients with ISR that are managed conservatively.

According to our results, conservative management could be considered in asymptomatic or mildly symptomatic patients with ISR, especially in those who were smokers and those who presented with an acute coronary syndrome at the time of coronary stenting.

Nevertheless conclusions of the study are limited by its retrospective nature and short sample size, therefore we can only make hypothesis regarding probably related clinical variables and treatment of ISRLR.

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