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Predictors of In-Stent Restenosis after Coronary Angioplasty

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Abstract **Original Research Article**

Background: Stents represent a major improvement for the coronary revascularization. However, restenosis (ISR) remains an important complication as it limits its effectiveness and may require new therapeutic interventions. The aim of our study is to define the predictive factors of this phenomenon. ***Material and methods:*** It is a retrospective study of 83 patients admitted in the cardiology department of the Military Hospital Avicenna in Marrakech during 2 years, who underwent coronary angioplasty and stenting. We have compared two groups of patients: 18 with restenosis (ISR+) and 65 without restenosis (ISR-). ***Results:*** The prevalence of ISR is 21.1%. The mean age is 59, 10 years. The population of ISR is characterized by high rate of diabetes (p: 0, 0001), the cumulation of more than 3 coronary risk factors (p: 0,0027). Stenting have interested the left anterior descending artery (LAD) in 52.2% of cases among the group with restenosis (p: 0, 0008).The stented lesions in RIS+ group are complex (p: 0,03) and lengthy (p : 0,04). Long stents were the most implanted (p: 0,0001). According to literature data, the independent predictive factors of restenosis in our study are diabetes (OR = 0.011), cumulative cardiovascular risk factors (OR = 0.027), lesions on the proximal LAD (OR = 0.03) and the use of long stents (OR = 0.01). ***Conclusion:*** At the end of our study, we can identify a group of high-risk patients who actually benefit from the use of active stents, which currently reduce the occurrence of restenosis.

Keywords: Restenosis (ISR); Angioplasty; Stent; Predictive factors.

INTRODUCTION

Coronary stents have opened wider perspectives for the percutaneous treatment of coronary disease, including the extension of angioplasty indications to multitroncular patients with chronic occlusion or complex lesions. However, the long-term outcome of stent implantation remains significantly constrained by the risk of developing in-stent restenosis (ISR) over time. The implantation of a stent remains burdened with a restenosis rate of the order of 20 to 30% [1]. After stenting, the phenomenon of constrictive remodeling is almost non-existent and restenosis, when it occurs, is essentially due to an neointimal tissue proliferation [2]. Although rarely resulting in acute coronary syndromes or deaths, in stent restenosis is a source of repeat readmissions and angioplasties, which leads to increased morbidity and additional costs. This phenomenon is therefore a new pathology that poses serious problems in daily practice regarding its treatment and especially its prevention and as it is true that the best therapeutic option in this situation is still questionable and continues to remain a challenge.

It seemed interesting to focus on this subject. In this context, we conducted this study to determine the various factors that predict the occurrence of ISR after coronary angioplasty and the factors associated with its recurrence.

METHODS

Population

This is a retrospective study of the type of control case, conducted over a period of 2 years, between January 2016 and December 2017. The study population is represented by patients admitted to the cardiology department of Avicenna Military Hospital of Marrakech, and having undergone a coronary angioplasty with stent use. We collected 83 patient files, 18 of which revealed an ISR. These cases (18 cases) represented by the patients who presented restenosis (ISR +) are compared to controls (65 cases) represented by the restenosis-naive patients (ISR-) population. Patients lost to follow-up, who died during the hospital phase or who had unsatisfactory angiographic results after stenting were excluded.

Parameters studied

Clinical and echocardiographic parameters were analyzed as well as angiographic data during stent implantation. It concerned the location and the number

of lesions, their complexity; the number of implanted stents, their type and dimensions. In the population presenting the ISR, the severity and type of restenosis were also studied. All our patients received regular follow-up in the first month after the procedure and then every three months.

Definitions

Restenosis is defined angiographically by a stenosis within the stented segment or its edge (5-mm segments adjacent to the stent) of >50% of the vessel diameter as determined by coronary angiography .The clinical definition of ISR requires the presence of >50% diameter in-stent stenosis and one of the following: clinical symptoms of recurrent angina, objective signs of ischemia, positive coronary hemodynamic assessment with fractional flow reserve (FFR) <0.80, or restenosis with ≥70% reduction in lumen diameter even in the absence of clinical symptoms or signs[3].

Mehran's classification describes four types of restenosis (pattern I: focal, pattern II: diffuse, pattern III: proliferative, and pattern IV: occlusive). This classification, initially proposed with bare metal stents (BMS), is still used to characterize restenosis after drug-eluting stents (DES) [4].

Statistical methods

The data was entered using Excel software and analyzed using SPSS software version 19.0. The descriptive analysis consisted of calculating the absolute and relative frequencies for the qualitative variables, and the positioning and dispersion parameters for the quantitative variables (mean standard deviation). In bivariate analysis, the comparison of qualitative variables used the Pearson Chi2 statistical test and the Fisher statistical test if necessary. The Student t-test or Mann Whiteny test were used to compare continuous variables. Multivariate binary logistic regression analysis was used to model the predictors of restenosis in patients who benefited from stent placement. Variables whose association was significant at the 20% threshold in bivariate analysis were included in a multivariate model. The variables retained in the final model were selected using a stepwise forward method with a threshold entry of 0.2 and a threshold exit of 0.05. Hosmer Lemeshow's test was used to examine the quality of the final logistic regression model. The threshold of significance was retained for $p < 0.05$.

RESULTS

The study involved 83 patients, 18 of whom presented with ISR. The occurrence of ISR was 21.7%. The clinical characteristics of the included patients are shown in Table 1. The average age of patients with ISR was similar to that of the control group with no significant difference. The majority of patients were under the age of 60 years with male predominance. The average number of cardiovascular risk factors per patient was 1.7. The ISR + group were characterized by a more significant rate of diabetes (55.5% versus 40%), hypertension (38.9% vs. 15.7%), accumulation of more than 3 factors risk (55% versus 18%) and chronic renal failure (26% vs. 3.3%). In contrast, smoking and dyslipidemia are similarly distributed in both groups.

The initial conditions of implantation in the ISR + group were as follows: ST-elevation myocardial infarction (STEMI) in 55.5%, non-ST-elevation myocardial infarction (NSTEMI) in 33.3% and stable angina in 11.1% without significant difference with the ISR- group. ISR + patients had left-ventricular failure in 33.3% of cases with significant difference ($p = 0.006$). The left ventricular ejection fraction was 50.6% in the ISR + group vs 56% in the naive group of ISR with no significant difference.

The coronary lesions were essentially monotroncular with a more significant level of tritroncular coronary lesions in the ISR + population (11% vs 7.4%, $p = 0.069$). The stented lesions in the ISR + group were significantly more complex (type B2 and C: 52% versus 25%) (Graph 1), longer (44.4% versus 3%) and interesting mainly small arteries (48, 6% vs. 36.1%). In addition, the rate of chronic occlusion was similar in both groups. ISR + patients had a higher rate of bifurcations, calcifications, angulations and intracoronary thrombi, compared to ISR- patients, with no significant difference (Table 2).

Angioplasty was performed in an emergency setting in 72.2% of cases in ISR + patients versus 55% in ISR- patients ($p = 0.029$). Stent implantation mainly concerned left anterior descending artery (LAD) (52.2% ISR + vs 40% ISR-, $p = 0.0008$), especially the proximal LAD (21.1% vs 10.3%, $p = 0.0003$). In both groups of patients, a DES implantation was performed in the majority of cases. Long stents (> 15 mm) were more used in patients with ISR compared to the control group (61.5% versus 19.3%, $p = 0.04$). The average stent release pressure was 14 bars for both populations. Almost a quarter of patients with ISR + had at least two stents on the same artery with no significant difference from the ISR- group. No patient from both groups interrupted his antithrombotic treatment.

The time of the presentation of ISR was 9.6 ± 11 months, diagnosed by coronarography. The period of 3 to 6 months was the most concerned (Figure 2). The coronarography was performed under the following circumstances: STEMI in 21.3% of cases, NSTEMI in 28.5% of cases, stable angina in 40% of cases and silent ischemia (10%). The patients included in the study had 118 stents of which 25 were the site of an ISR. The prevalence of ISR was 21.1% (16.6% for DES and 30% for BMS). The angiographic features of ISR lesions are shown in Table 3. Restenosis occurred at stents implanted mainly on LAD (50% of cases). Most ISR

lesions were diffuse (72.7%), and they were focal in 27.2 % of cases.

The majority of ISR + patients received a second revascularization procedure (Table 4). For 22 ISR lesions (88%), the proposed therapy was a new coronary angioplasty; balloon alone in 28% of cases and repeat stenting in 56% of lesions. Coronary artery bypass was performed in two cases with proliferative restenosis. The recurrence of ISR after successful interventional treatment involved four lesions treated for restenosis (16%) and the recurrence time was 7.5 +/- 5.6 months.

Predictors of restenosis in univariate analysis

Several factors analyzed were associated with a statistically significant difference between the two populations (Table 5). Indeed, the risk of restenosis has been increased in hypertensive and diabetic patients with more than three cardiovascular risk factors, chronic renal failure and those admitted with heart failure. Similarly, patients who have undergone angioplasty in an emergency setting have a risk of increased restenosis. On the other hand, age, gender, other cardiovascular risk factors, including tobacco; although it is the most frequent risk factor; and the initial conditions of implantation, do not seem to influence the probability of restenosis.

The stent implantation on the LAD especially as it is located at the proximal segment was also very significant. There is also a trend towards the significance (p = 0.069) of the tritroncular status, to predict the occurrence of an ISR. Complex, long lesions with a diameter <2.75mm also increased the risk of restenosis. The same is for the length of the stent used (> 15mm). The number of stents and the number of stented lesions did not influence the probability of restenosis. In comparing patients who had been treated with DES, 16.6% had ISR vs 30% treated with a BMS. However, in univariate analysis, the use of a BMS is not a risk factor for the occurrence of restenosis in our series (p = 0.1).

Predictors of restenosis in multivariate analysis

The different predictors of ISR identified in univariate analysis were integrated into a binary logistic regression model. The analysis of each identified variable predicting restenosis in the bivariate analysis compared to the other variables concluded four independent and powerful predictors of ISR: diabetes (OR = 0.011), cumulative cardiovascular risk factors (OR = 0.027) , stented artery seat at the proximal LAD (OR = 0.03) and use of long stents (OR = 0.01) (Table 6).

Predictive factors for recurrence of ISR

In univariate analysis, unstable angina, diffuse ISR, a short delay of ISR less than or equal to 3 months and diabetes are the predictors of recurrence of restenosis. However, the therapeutic method is not associated with the recurrence of ISR. In multivariate analysis, only the short duration of the ISR represents the independent predictor of recurrence of restenosis (Table 7).

Table-1: Clinical characteristics of patients

Variable		ISR+	ISR -	*P*
Average age		59,4± 10 years	59,10 ± 10 years	NS
Age	<60 years	61,5%	61%	0,97(NS)
	≥60 years	38,5%	39%	
Tobacco		72,2%	70,7%	0,90(NS)
HTA		38,9%	15,7%	0,04
Diabetes		55,5%	40%	0,0001
Dyslipidemia		16,7%	15%	0,11(NS)
> 3 cardiovascular risk factors		55%	18%	0,0027
CKD		26%	3,3%	0,006
Initial clinical presentation				
Stable Angina		11,1%	8,7%	NS
STEMI		55,5%	52,4%	NS
NSTEMI		33,3%	38,9%	NS
Left heart failure		33,3%	6%	0,006
Angioplasty in an emergency context		55%	72,2%	0,029

Table-2: Angiographic lesions features

Coronary lesions	ISR-	ISR+	P
Coronary status			
Monotroncular	64,8%	62,8%	NS
Bi-troncular	27,8%	26,2%	NS
Tritroncular	7,4%	11%	0,069
Seat			
LAD	40%	52,2%	0,0008
LADproximal	10,3%	21,1%	0,0003
CX	17,3%	12,2%	NS
CD	36,5%	31,1%	NS
Diagonal	3.5%	2.2%	NS
Marginal	2.7%	2.2%	NS
Qualitative analysis			
Bifurcation	14,8%	15,8%	NS
Thrombus	7,9%	18,5%	NS
Calcifications	18%	23,7%	NS
Angulation>45	14%	15,6%	NS
Length >15mm	44,4%	3%	0.04
Reference diameter <2,75mm	36,1%	48,6%	0,038
Chronic occlusions	5,3%	6,7%	NS
Stent length >15mm	19,3%	61,5%	0,0001
Stented lesions			
1 stent by artery	82,4%	73,3%	NS
2 stents by artery	15,6%	23,3%	NS
3 stents by artery	2%	3,3%	NS
Stent type			
Bare stent	29%	48%	NS
Active stent	69%	52%	NS

Table-3: Angiographic features of ISR lesions

ISR lesions	Percentage
Seat	
LAD	50%
CD	31%
CX	16%
Diagonal	2%
Marginal	1%
Focal	27,2%
type Ia	0%
type Ib	50%
type Ic	16,6%
type Id	33,3%
Diffuse	72,7%
type II	25%
type III	37,5%
type IV	37,5%

Table-4: Therapeutic modalities of in-stent restenosis

Treatment	Size	Percentage	Evolution
Balloon	7	28%	1recurrence of restenosis.
Bare stent	1	4%	Recurrence of restenosis.
Active stent	14	56%	2recurrence of restenosis.
Surgery	2	8%	Good evolution
Enhanced medical treatment	1	4%	Good evolution

Table-5: Predictors of restenosis in univariate analysis

Variable	$\chi 2$ Test or Fisher test	*p*
HBP	3,995	0,04
Diabetes	24,39	0,0001
CKD	F	0.006
>3cardiovascular risk factors	9,015	0,0027
Left heart failure at admission	F	0,006
Angioplasty in an emergency context	F	0,029
LAD stented artery seat	13,11	0,0008
LAD1 stented artery seat	11,338	0,0003
Complex lesions	4,234	0,03
Lesion length > 15mm	4,124	0,04
Artery diameter reference <2,75mm	F	0,038
Long stents (length > 15mm)	15,648	0,0001

Table-6: Predictive variables of ISR according to the binary logistic regression model

Independent variables	β	$\chi 2$	*p*	OR (CIat 95,0%)
Diabetes	0,025	0,616	0,011	3,2 (2,83-6,06)
> 3 cardiovascular risk factors	0,138	0,676	0,027	1,3 (1,82-2,59)
LAD1 stented artery seat	1,065	2,312	0,03	2,9(1,7-4,12)
Long stents (length > 15mm)	0,912	1,651	0,01	3,1(2,8-5,81)

β: Bêta, $\chi 2$: Wald, p: degree of significance of the Wald test, OR: Odds Ratio, IC: confidence interval

Table-7: Predictors of the recurrence of restenosis

Predictive Factors for ISR Recurrence	OR [CI]	P	OR adjusted	P
Unstable angina	8 [0,6 - 69]	0,03		0 ,14
ISR diffuse	6,5 [0,7 - 56]	0,05		0,7
Early delay of ISR <3 months	11,6 [2,1 - 64]	0,006	19,4 [1,3 - 282]	0,03
Diabetes	3,8 [1,01 -14,9]	0,04		0,3

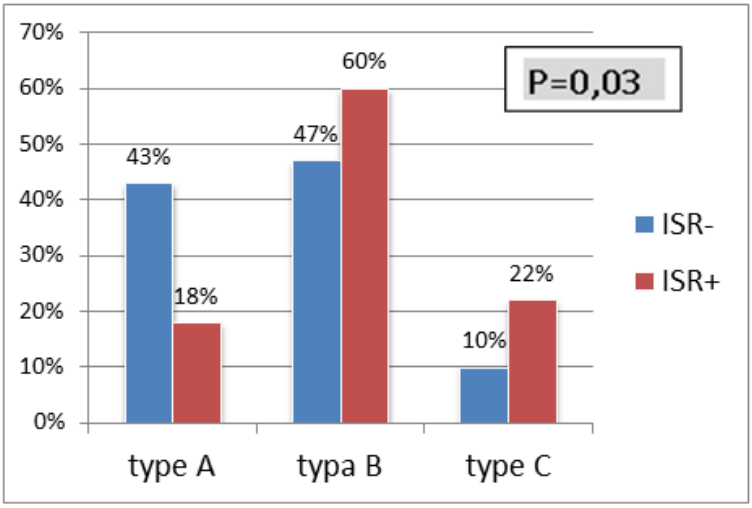

Fig-1: Classification of the complexity of coronary lesions

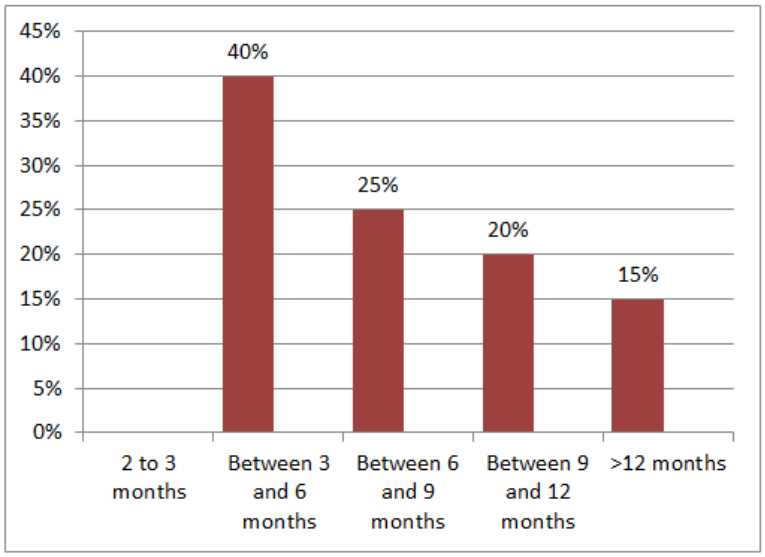

Fig-2: ISR delay

DISCUSSION

For many years, restenosis has been a challenging problem. Although the systematic use of DES stents has led to improvement in patients' clinical and procedural outcomes, the long-term outcome remains significantly constrained by occurrence of ISR; the rate of angiographic restenosis remains about 12% (20-30% for BMS) in larger registers. In our series, the prevalence of ISR was 21.7%. Its management remains complex and the constant increase of angioplasties and the treatment of more and more complex lesions explain why it has not deserted our coronarography rooms. More serious, this restenosis remains an independent factor of mortality. Most studies agree that ISR in DES is certainly rarer but more serious than ISR in BMS with; in particular, more frequent unstable clinical presentation [5].

In-stent restenosis is a neointimal proliferation associated with increased production of extracellular matrix. Intimal hyperplasia is associated with a process of re-endothelialization [6-9]. It can also be caused by in-stent neoatherosclerosis. Unlike native atheroma, neo-atheroma develops more rapidly after stent implantation. The development of neoatheroma seems earlier and more frequent with DES than with BMS. The restenosis we are facing is probably very different from the one we used to look for with increased thrombotic potential [10].

The majority of ISR occur within 6 months of the procedure [12]. It rarely occurs before the 2nd month, and exceptionally after the 9th month [12]. In our study, the average time of its occurrence is 9.6 months. Two-thirds of our patients develop clinical restenosis before the 9th month after the procedure and late angina recurrence is mainly related to a new lesion.

In our series, the clinical presentation of ISR involves the presence of angina symptoms, only 10% were asymptomatic. These results are very similar to those of the literature [13-16].

ISR must be considered as a polymorphic and multifactorial process. In accordance with literature data, the analysis of our series individualized several patient, lesion-and procedural-related factors as predictive of restenosis. However, four parameters in multivariate analysis: diabetes mellitus, cumulative cardiovascular risk factors, stent implantation in the proximal LAD, and use of long stents were identified as the strongest independent predictors of restenosis.

It is clear that all studies agree that diabetes mellitus has a major role in determining and foster the ISR process [17, 18]. The mechanisms responsible for increasing the propensity for ISR in diabetic patients are not completely understood. In an IVUS analysis, it was concluded that the main reason was exaggerated intimal hyperplasia in stented and unstented lesions [18]. However, the data according to Van Belle *et al*. [19] do not support this hypothesis, but rather promote constrictive remodeling as the main mechanism. The prothrombotic milieu typical of diabetic coronary vessels, abnormalities in extracellular matrix production, endothelial dysfunction and increased production of growth factors may also be an important determinant in this phenomenon [20].

In our series, the accumulation of more than three cardiovascular risk factors is an independent factor of ISR (OR = 1.3). Our results are very similar to those of Weintraub [21], who in a series of 4006 patients who benefited from stenting with coronary arteriography within 6 months, demonstrated that patients with high cardiovascular risk had more ISR (p = 0.015).

Our series identified other clinical factors associated with an increased risk of ISR in univariate analysis including hypertension, chronic kidney disease (CKD), left ventricular failure, and angioplasty in an emergency setting. Kastarati [22], which in a large series including 4510 patients, shows that hypertension is independently correlated with angiographic ISR at 6 months with an OR of 1.21 (p = 0.009).

Concerning the CKD, There are few published series that have focused on ISR in this population. They are often monocentric retrospective at low levels. In addition, the results are contradictory.

For some, CKD does not appear to be a risk factor for clinical ISR [23, 24]. On the other hand, other studies conclude that this population seems to have high levels of ISR [25, 26]. In our series, the CKD (clearance of creatinine <30ml / min) is associated in univariate analysis with the ISR (p = 0.006). However, because of the small size of this subgroup, ISR remains dependent on other risk factors, especially diabetes.

In addition, Kastarati [22] showed that coronary angioplasty in a period of instability is a predictor of restenosis. Similarly, our study showed similar results (p = 0.029). The other clinical variables predictive of restenosis less consistently found, including age [22], initial acute coronary syndrome [27, 28] do not emerge as predictors in our series.

Many studies are contradictory about LAD stenting as a predictor of ISR. However, most often, it is claimed that LAD lesions are more prone to restenosis. In a study of 2500 patients treated with balloon [21], proximal LAD lesions had an OR of 1.7 compared to non-proximal LAD. Another follow-up analysis of 1,399 lesions demonstrates that LAD stenting is an independent predictor of ISR at 6 months with an OR of 1.31 [22] as is the case in our series. On the other hand, others do not find a significant relationship between the two [29].

Our study is consistent with several series that have demonstrated that stent length and more precisely the length of the segment covered by metal is positively correlated with late lumen loss. Kobayashi *et al*. [30] demonstrated in an analysis of 1,090 lesions in 725 patients that progressive stent length is associated with increased ISR risk, with six-month rates of 24%, 35%, and 47% for stent's lengths of 20, .20 to 35 and 35 mm. In another analysis of four Multi-Link stent assays [31], stent length was found to be a significant predictor in both univariate and multivariate analyzes, and for every millimeter of increase in the length of the stent, there was an OR of 1.04 for the development of restenosis.

Other factors have been identified in our series as predictors of ISR in univariate analysis: complex and long lesions besides a small vessel caliber [22, 27, 29]. Indeed, Kastrati (22) in a study involving 2944 patients whose 81% had angiographic control at 6 months after stent implantation, demonstrated that complex lesions independently predict ISR with frequency of 33.2% for type B2 / C lesions and 24.9% for type A / B1 lesions (p <0.001). The lesion length is also a predictive factor of ISR found almost in all studies including that of Kastrati (22) who compared two groups of patients: 573 patients with lesions> 15 mm and 2163 patients with lesions <15 mm. He found a significantly higher 6-month ISR rate in the long-lesion group (36.9% vs 27.9%, p <0.001). Small vessels are more predictive of ISR because of reduced ability to adapt the intimal response following arterial trauma [29, 32].

Other variables consistently found in the literature include, chronic occlusion, the number of stented lesions and the number of stents per lesion [29, 32] is not associated with an increase in ISR risk in our series. The quality of the immediate result, expressed in angiography, by the minimum luminal diameter and which is a determining factor in the occurrence of ISR, has not been studied in our series [22, 33]. Procedural factors, including stent overlap and malapposition, result in a significant neointimal hyperplasia reaction and are therefore ISR factors [22]. In our study, these factors have not been studied.

The treatment of patients with ISR continues to remain a challenge and can use several techniques. The effectiveness of these different methods has already been widely reported in the literature. In our center, only some of them were available and were used. Currently available options include angioplasty alone; repeat stenting with DES or drug-coated balloons (DCB).

Balloon angioplasty is a very simple technique and one of the first techniques used to treat the BMS restenosis. The results are satisfactory for focal restenosis, but disappointing for diffuse restenosis. In the Mehran study [34], the secondary revascularization rate is 19% for focal restenosis and 83% for occlusive restenosis. In our study, the recurrence of ISR after ballooning is seen in 20% of cases. Active balloons (DCB) have been shown to be effective in ISR, superior to the balloon alone and comparable in efficacy to first-generation active stents. However, the minimum luminal diameters were higher with the installation of new second-generation DES. Current clinical data suggest that among various available therapeutic modalities, second-generation DES and DCB provide the best clinical and angiographic results in patients with ISR.

The use of DES was quickly the treatment of choice for in-stent restenosis with greater efficiency in terms of angiographic results as well as clinical outcomes [35]. In our study, 56% of the lesions were treated with a DES. The recurrence rate of restenosis

was 12.5%. Coronary bypass still present in coronary revascularization even after ISR. Nevertheless, the recurrence rate was higher after percutaneous techniques (33% vs 8%, p = 0.05) [36]. In our series, two patients were operated for ISR because they were tritroncular with proliferative restenosis.

CONCLUSION

Although restenosis has become a very rare complication in the era of systematic use of DES, it still represents "the present" and not "the past" of interventional cardiology. It is an independent predictor for mortality during follow-up.

At the end of our study, we were able, according to the literature data, to identify a group of patients at high risk of ISR. These risk factors have fully benefited from DES to reduce the occurrence of ISR. However, ISR is a still open challenge also in the DES era and its management remains complex as well as the new pathophysiology associated, makes the restenosis that we face is probably very different from the one we used to look for.

If the possibilities of treatment are multiple, this last one must probably be individualized and just like DES, DCB is currently the first choice treatment for this complication, both in case of BMS or DES restenosis.

Conflicts of interest

The authors do not declare any conflict of interest.

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