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Early and late restenosis of drug-eluting stents: an observational study about predictors, clinical presentation and response to treatment (the LATE DES study)

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KEYWORDS

- acute gain
- coronary angioplasty
- drug-eluting balloon
- drug-eluting stent
- in-stent restenosis
- late lumen loss

Abstract

Aims: The aim of the study was to evaluate differences in clinical presentation, angiographic and clinical predictors, and response to treatment of early (<9 months) vs. late (≥9 months) in-stent restenosis (ISR) of drug-eluting stents (DES).

Methods and results: One hundred and twenty-nine patients with DES restenosis (defined by angiography as diameter stenosis >50% at the stent segment or its edges) were enrolled: 79 (61%) had early DES restenosis (6±2 months) and 50 (39%) late DES restenosis (18±8 months). ISR treatment strategy was left to the operator's choice: DES or drug-eluting balloon (DEB). The primary endpoint was the incidence of major adverse cardiovascular events (MACE) at follow-up. Patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure as compared to those with late DES restenosis (OR 2.63, 95% CI: 1.12-6.25; p=0.027). The treatment of DES restenosis was DES implantation in 78 (60%) patients and DEB in 51 (40%) patients, without differences between early and late DES ISR. MACE after ISR treatment occurred in 25 (19%) patients, without differences between early and late DES ISR (16 [20%] vs. 9 [18%]; p=0.75, respectively). Diabetes mellitus was the only independent predictor of MACE at follow-up (OR 4.6, 95% CI: 1.3-19.3; p=0.03). MACE-free survival was similar after treatment in early or late ISR (p=0.097) and according to ISR treatment (p=0.73).

Conclusions: Early DES restenosis occurred more frequently after DES implantation for ACS compared with late DES restenosis. This, however, did not translate into a difference in MACE rate after ISR treatment at follow-up. Treatment choice for ISR did not affect prognosis. Diabetes mellitus remains the only independent predictor of MACE after treatment of DES ISR.

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Introduction

Drug-eluting stents (DES) were introduced into clinical practice with the primary purpose of reducing the incidence of in-stent restenosis (ISR). Indeed, ISR has emerged as a relevant drawback related to the implantation of bare metal stents (BMS), largely limiting their efficacy because of an incidence of up to 30%. Initial trials evaluating the safety and efficacy of DES in non-complex coronary lesions showed an impressively low rate of ISR (<10%)[1,2]. However, despite exciting results being reported during the initial trials evaluating the safety and efficacy of first-generation DES, the real-world use of DES, often in complex coronary lesions (such as bifurcations, saphenous vein graft, chronic total occlusion), has clearly shown that ISR still occurs after DES implantation, depending on clinical, lesion- and procedure-related factors[3]. In particular, the occurrence of late stent ISR has emerged as an important issue related to DES implantation. Indeed, some studies have raised the possibility of a late catch-up phenomenon[4-8], as if antiproliferative drugs might simply delay the occurrence of ISR, the temporal window of DES restenosis presentation being wider compared with that of BMS. Yet, studies evaluating clinical presentation, angiographic and clinical predictors, and response to treatment of early vs. late ISR are still lacking. Of importance, pathogenic mechanisms of early and late ISR of DES may be different. In particular, early ISR seems to be related to procedural factors, while late ISR may be associated with an individual susceptibility, with a delayed arterial healing and a persistent inflammatory response to the stent polymer (hypersensitivity reaction)[7,8]. Furthermore, several studies have reported that neoatherosclerosis may play an important role in late ISR[9,10]: histological and *in vivo* imaging studies show that neoatherosclerosis consists of an accumulation of lipid foamy macrophages within the neointima with or without necrotic core formation and calcification[11,12].

Our study aimed to evaluate differences in clinical presentation, angiographic and clinical predictors, and response to treatment of early (<9 months) vs. late (>9 months) ISR of DES.

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Methods

STUDY DESIGN AND CLINICAL ENDPOINTS

The LATE DES study is a registry which enrolled patients presenting with DES restenosis between January 2009 and June 2011 in 15 centres across the Rome area **(Figure 1)**. DES restenosis was defined by angiography as recurrent diameter stenosis >50% at the stent segment or its edges (5 mm segments adjacent to the stent). Each centre decided to enrol patients respecting the exclusion criteria which were: surgical or medical management to treat DES restenosis (n=15); known hypersensitivity reactions towards materials or components used in percutaneous coronary intervention (PCI) (n=7); suspected low compliance to dual antiplatelet therapy (e.g., planned surgical interventions, bleeding risk) (n=12); DES restenosis of a stent implanted in overlap with a different stent (n=10); pregnancy (n=2); life expectancy <12 months (n=9); previous history for treated ISR (n=17).

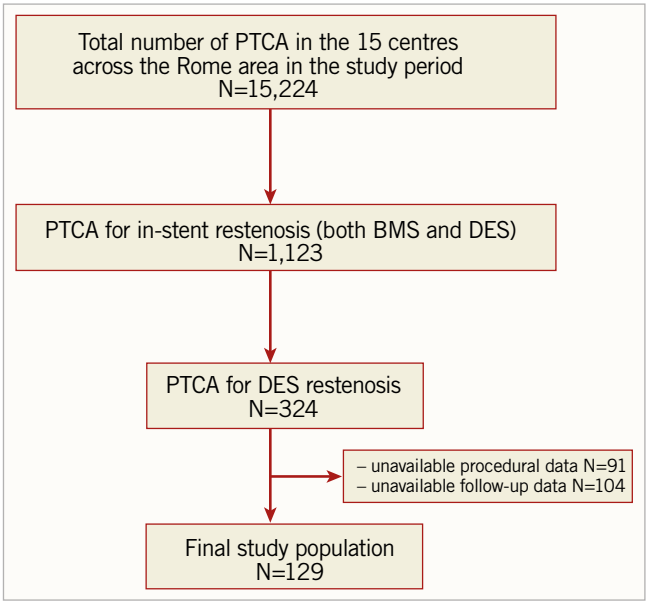

Figure 1. *Flow chart showing the origin of the sample size of the study.*

Post-index coronary angiography was performed because it was clinically driven either due to recurrent angina or to evidence of ischaemia by stress test.

Clinical and procedural data of both ISR PCI and the previous PCI in which the DES was implanted were recorded. The treatment strategy for ISR was left to the operator's choice: DES (first- or second-generation) or drug-eluting balloon (DEB). Case report forms were completed at each site by local investigators and submitted to the coordinating centre (Policlinico A. Gemelli, Rome, Italy). Data were monitored and reviewed for completeness and consistency. When required, specific queries were sent back from the coordinating centre to the sites. Patient follow-up was performed by telephone or clinic visit at one, six and 12 months. The primary endpoint was the incidence of major adverse cardiovascular events (MACE), defined as the composite of death from cardiac causes, non-fatal myocardial infarction (MI), clinically driven target vessel revascularisation (TVR) or rehospitalisation due to unstable or progressive angina according to the Braunwald unstable angina classification[13]. Cardiac death was ascertained by contacting the family doctor or the hospital where the patient died. MI was diagnosed by detection of rise and fall of cardiac biomarkers (preferably troponin) above the 99th percentile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following: ischaemic symptoms; electrocardiographic changes indicative of new ischaemia (new ST-T changes or new left bundle branch block); development of pathological Q-waves in the electrocardiogram; imaging evidence of new loss of viable myocardium or new regional wall motion abnormalities. TVR was carried out in the presence of a diameter stenosis >50% in the culprit vessel in patients with recurrence of symptoms and/or evidence of inducible myocardial ischaemia. Target

lesion revascularisation (TLR) was defined as either repeat percutaneous or surgical revascularisation for a lesion anywhere within the stent or the 5 mm borders proximal or distal to the stent. All planned staged procedures in patients with multivessel disease were performed during the index admission and were not included in MACE. The protocol indicated that, during follow-up, all repeat interventions were required to be clinically justified. The Academic Research Consortium definition was used to assess the presence of stent thrombosis.

The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of each enrolling centre.

ANGIOGRAPHIC ANALYSIS

All coronary angiograms were analysed at the angiographic core laboratory by trained personnel blinded to clinical characteristics and timing of restenosis by using standard methodology. The analyses were performed at the coordinating centre (Policlinico A. Gemelli, Rome, Italy). The Mehran and the modified American College of Cardiology/American Heart Association classifications were used to assess lesion morphology[14,15]. An automatic edge-detection system (CASS II System; Pie Medical, Maastricht, the Netherlands) was used for offline quantitative measurements. Carefully selected orthogonal, angiographic views (without vessel foreshortening or side branch overlap) were obtained after nitroglycerine administration. Matched projections were repeated after intervention and at follow-up. In-lesion and in-segment (the treated segment plus 5 mm proximal/distal margins) analyses were performed. Reference vessel diameter, minimal lumen diameter, percent of diameter stenosis, late loss, loss index, and binary restenosis rate (>50% diameter stenosis) were determined.

STATISTICAL ANALYSIS

Data distribution was assessed according to the Kolmogorov-Smirnov test. Continuous variables were compared using an unpaired Student's t-test or Mann-Whitney U test, as appropriate, and data were expressed as mean±standard deviation or as median (range). Categorical data were evaluated using the chi^2 test. Univariate logistic regression analysis was performed to evaluate predictors of early vs. late DES ISR.

Since the "right censoring" condition applies for the follow-up data, a Cox proportional hazard ratio (HR) model has been used for the survival analysis. Event-free survival was measured from the date of discharge to the occurrence of a MACE or to the date of last follow-up evaluation at one year. Thus, as primary analysis, we performed a simple Cox regression analysis using all variables on their original continuous scale to estimate the unadjusted HRs of all variables. We also calculated the 95% confidence interval (CI) of the coefficient of the Cox regression. Adjusted HRs were calculated by including in the multivariable Cox regression analysis model variables showing p≤0.15 at univariate Cox regression analysis and the variables age and sex because they were considered biologically relevant. The validity of the proportional hazards assumption was tested adding a time-dependent interaction variable for each of the predictors, and estimates of the C-index for the Cox regression model were calculated. Survival curves using the Kaplan-Meier method were produced for the occurrence of MACE according to the early or late ISR and to the treatment choice for ISR (DES or DEB) and compared by the log-rank test.

All tests were two-sided and a p-value of <0.05 represented statistically significant differences. All analyses were performed using SPSS, Version 20 (IBM Corp., Armonk, NY, USA).

Results

CLINICAL, PROCEDURAL AND ANGIOGRAPHIC CHARACTERISTICS OF PATIENTS WITH EARLY VS. LATE DES RESTENOSIS

The clinical characteristics of the overall study population and according to the presence of early or late DES restenosis are listed in **Table 1**. One hundred and twenty-nine patients with DES restenosis were enrolled (mean age 66±9 years, 84 [65%] male). Seventy-nine (79; 61%) patients presented with early (6±2 months) DES restenosis and 50 (39%) patients with late (18±8 months) DES restenosis. No differences in risk factors, angiographic and procedural variables were detected between the early and late DES restenosis groups. Of importance, patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure compared with late DES restenosis (66 [84%] vs. 33 [66%], p=0.027) **(Figure 2)**. No differences were found in clinical presentation of DES restenosis between early and late DES ISR. Moreover, angiographic patterns of in-stent restenosis, according to the Mehran classification, did not differ between the two study groups.

Of note, at univariate logistic regression analysis, ACS as clinical presentation at the index procedure was the only predictor for early vs. late DES restenosis (OR 2.63, 95% CI: 1.12-6.25; p=0.027). Quantitative coronary angiography (QCA) data of the index and ISR procedures are reported in **Table 2** and show no significant differences between early and late DES ISR.

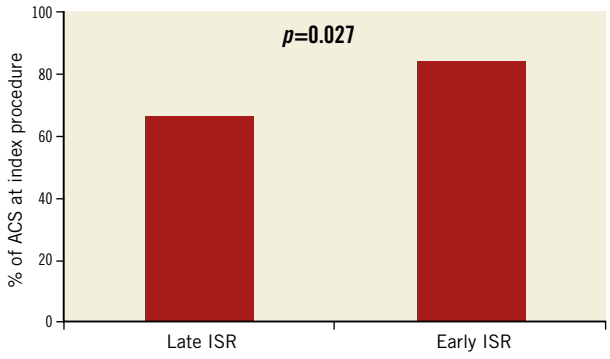

Figure 2. *Prevalence of acute coronary syndromes (ACS) at index procedure according to timing of ISR (early vs. late).*

Table 1. Baseline clinical, angiographic and procedural characteristics in the overall population and according to the timing of restenosis.

		Overall (n=129)	Restenosis >9 months (n=50, 39%)	Restenosis ≤9 months (n=79, 61%)	*p*-value
Clinical variables					
Age, years, mean±SD		66±9	67±9	65±10	0.31
Male, n (%)		84 (65)	32 (64)	52 (66)	0.83
Risk factors	Hypertension, n (%)	90 (70)	35 (70)	55 (70)	0.96
	Hypercholesterolaemia, n (%)	72 (56)	27 (48)	45 (60)	0.74
	Diabetes mellitus, n (%)	49 (38)	20 (40)	29 (37)	0.71
	Active smoking, n (%)	28 (22)	12 (24)	16 (20)	0.61
	Family history of CAD, n (%)	36 (28)	10 (20)	26 (33)	0.11
	Chronic kidney disease, n (%)	9 (7)	3 (6)	6 (8)	0.73
	Body mass index, mean±SD	27±5	26±3	27±5	0.40
Clinical presentation at index procedure	Stable angina, n (%)	30 (23)	17 (34)	13 (16)	0.027
	ACS, n (%)	99 (77)	33 (66)	66 (84)	
Clinical presentation of ISR	Stable, n (%)	104 (81)	41 (82)	63 (80)	0.75
	ACS, n (%)	25 (19)	9 (18)	16 (20)	
Procedural and angiographic variables of the index procedure					
Target vessel	LMS, n (%)	3 (2)	1 (2)	2 (2.5)	0.96
	LAD, n (%)	70 (54)	29 (58)	41 (33)	
	LCX, n (%)	29 (22)	10 (20)	19 (15)	
	RCA, n (%)	25 (19)	9 (18)	16 (12)	
	SVG, n (%)	2 (1.5)	1 (2)	1 (1)	
Lesion type	A, n (%)	28 (22)	10 (20)	18 (14)	0.91
	B, n (%)	39 (30)	16 (32)	23 (18)	
	C, n (%)	62 (48)	24 (48)	38 (29)	
Stent implantation procedure	DES type, n (%)				0.21
	First-generation	71 (55)	31 (62)	40 (51)	
	Paclitaxel-eluting stent	31 (44)	14 (45)	18 (45)	
	Sirolimus-eluting stent	40 (56)	17 (55)	22 (55)	
	Second-generation	58 (45)	19 (38)	39 (49)	
	Zotarolimus-eluting stent	27 (47)	10 (53)	19 (49)	
	Everolimus-eluting stent	31 (53)	9 (47)	20 (51)	
	Stent length, mm, mean±SD	27.4±14.7	27.7±15.9	27.4±13.6	0.92
	Stent diameter, mm, mean±SD	2.9±0.4	2.9±0.3	2.9±0.5	0.94
	Stent pressure, atm, mean±SD	15.0±2.2	15.2±2.2	14.8±2.3	0.38
	Balloon post-dilation				
	Performed, n (%)	94 (73)	33 (66)	61 (47)	0.16
	Balloon diameter, mm, mean±SD	3.1±0.7	3.1±0.8	3.1±0.6	0.96
	Balloon pressure, atm, mean±SD	16.0±4.7	15.2±5.1	17.2±4.0	0.14
ISR treatment	DES, n (%)	78 (60)	29 (58)	49 (62)	0.71
	First-generation	30 (38)	14 (48)	26 (53)	
	Paclitaxel-eluting stent	14 (47)	6 (43)	12 (46)	
	Sirolimus-eluting stent	16 (53)	8 (57)	14 (54)	
	Second-generation	48 (62)	15 (52)	23 (47)	
	Zotarolimus-eluting stent	23 (48)	8 (53)	12 (52)	
	Everolimus-eluting stent	25 (52)	7 (47)	11 (48)	
DEB, n (%)		51 (40)	21 (42)	30 (38)	0.57

ACS: acute coronary syndrome; CAD: coronary artery disease; ISR: in-stent restenosis; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; LMS: left main stem; RCA: right coronary artery; SVG: saphenous vein graft

Table 2. Quantitative coronary angiography (QCA) results.

	Overall (n=129)	Restenosis >9 months (n=50)	Restenosis ≤9 months (n=79)	*p*-value
Baseline index procedure				
RVD, mm, mean±SD	2.7±0.4	2.8±0.4	2.7±0.3	0.32
Lesion length, mm, mean±SD	21.1±10.9	21.5±10.1	21.0±12.0	0.83
MLD, mm, mean±SD	0.7±0.4	0.6±0.4	0.7±0.4	0.51
DS, %, mean±SD	83±16	84±13	79±19	0.11
Post index procedure				
MLD, mm, mean±SD	2.4±0.5	2.4±0.5	2.4±0.5	0.95
DS, %, mean±SD	15±11	16±13	14±10	0.38
Acute gain, mm, mean±SD	1.9±0.6	1.9±0.6	1.8±0.7	0.77
Restenosis baseline				
RVD, mm, mean±SD	3.0±2.0	3.1±2.6	2.8±0.5	0.43
Lesion length, mm, mean±SD	15.1±9.1	15.2±9.0	14.5±8.2	0.73
MLD, mm, mean±SD	0.9±0.5	0.9±0.5	0.9±0.5	0.94
DS, %, mean±SD	77±15	76±15	77±16	0.82
LLL, mm, mean±SD	1.47±0.57	1.50±0.61	1.41±0.53	0.49
Restenosis pattern (Mehran classification)				
Focal, n (%)	73 (56%)	28 (56%)	45 (57%)	0.78
Diffuse, n (%)	56 (44%)	22 (44%)	34 (43%)	

DS: diameter stenosis; LLL: late lumen loss; MLD: minimal lumen diameter; RVD: reference vessel diameter

Table 3. Clinical outcome after DES restenosis treatment.

	Overall (n=129)	Restenosis >9 months (n=50, 39%)	Restenosis ≤9 months (n=79, 61%)	*p*-value
Cumulative MACE, n (%)	25 (19)	9 (18)	16 (20)	0.75
Cardiac death, n (%)	4 (3)	1 (2)	2 (2.5)	0.85
Non-fatal MI, n (%)	5 (4)	1 (2)	3 (3.5)	0.57
TVR, n (%)	13 (10)	6 (12)	7 (9)	0.56

MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularisation

CLINICAL OUTCOME FOLLOWING TREATMENT OF DES RESTENOSIS

The treatment of DES restenosis in the overall population was DES implantation in 78 (60%) patients and drug-eluting balloon (DEB) in 51 (40%) patients, without differences between early and late DES ISR **(Table 1)**. MACE after ISR treatment occurred in 25 (19%) patients in the overall population, without difference between early and late DES ISR (16 [20%] vs. 9 [18%], p=0.75, respectively). In addition, no differences were found according to early vs. late DES ISR for cardiac death, non-fatal MI and TVR **(Table 3)**. Moreover, no difference in MACE incidence was found according to the treatment strategy for ISR (DES vs. DEB). At univariate regression analysis, diabetes mellitus (HR 5.4, 95% CI: 1.4-21.3; p=0.016) and lesion length (HR 1.07, 95% CI: 1.01-1.41; p=0.030) were the only predictors of MACE **(Table 4)**. The presence of an early DES restenosis (HR 2.43, 95% CI: 0.88-7.69; p=0.092) was not significantly associated with MACE. Of importance, at multivariate regression analysis, diabetes mellitus was the only independent predictor of MACE at follow-up (HR 4.6, 95% CI: 1.3-19.3; p=0.03) **(Table 4)**. Finally, Kaplan-Meier analysis showed no significant difference in MACE-free survival after treatment according to early or late ISR (p=0.097) **(Figure 3A)** and according to ISR treatment (DES or DEB) (p=0.73) **(Figure 3B)**.

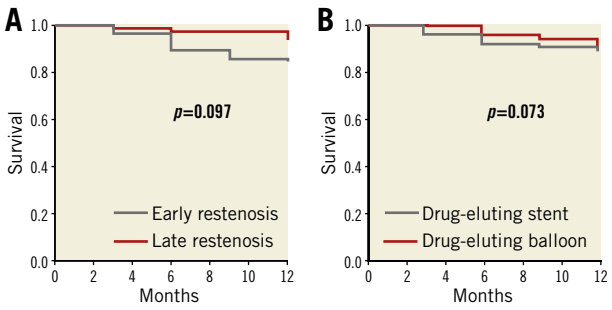

Figure 3. *Kaplan-Meier analysis showing MACE-free survival after ISR treatment. A) According to early or late ISR. B) According to treatment choice (DES or DEB).*

Discussion

The main findings of the LATE DES registry, one of the largest registries enrolling patients presenting with DES ISR, are the following: 1) patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure as compared to those with late DES restenosis; 2) MACE after ISR treatment at one-year follow-up occurred in 19% of patients in the overall population, without difference between early and late DES ISR or according to treatment choice for ISR (DES or DEB); 3) diabetes mellitus was the only independent predictor of MACE at follow-up after DES ISR treatment.

Table 4. Univariate and multivariate regression analysis.

	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Diabetes mellitus	5.4	1.4-21.3	0.016	4.6	1.3-19.3	0.03
Stenosis length	1.07	1.01-1.41	0.030			

Of importance, here we provide to the best of our knowledge the first evidence that early DES restenosis occurs more frequently in patients presenting with ACS at the index procedure as compared with late DES restenosis. Inflammation has been shown to play an important role both in atherosclerotic plaque progression and destabilisation and in ISR[9,16,17]. Indeed, DES were designed to obtain a site-specific delivery of drugs with anti-inflammatory and antiproliferative properties, in order to counteract the mechanisms leading to ISR[18]. However, patients presenting with ACS have a more pronounced local and systemic inflammatory activation compared with stable patients[19], probably not completely counteracted by the eluted drug, and possibly leading to early DES restenosis. On the other hand, in patients without ACS as clinical presentation, the eluted drug is able to counteract the inflammatory response following DES implantation and to prevent early ISR; late DES ISR may be mainly related to a chronic inflammatory response to polymer and/or neoatherosclerosis[9,10]. In addition to inflammation, other mechanisms may support our finding. For example, in the setting of ACS, the presence of thrombus and coronary hypercontractility may lead to implantation of an undersized stent, predisposing to restenosis.

Treatment of DES ISR is particularly challenging and associated with a poor outcome[20]. In our registry, one patient in five had experienced a MACE after DES ISR treatment at one-year follow-up. Of note, no differences were observed in MACE rate according to early or late ISR or according to the treatment for DES ISR (repeat stenting with DES or DEB). Initial observational studies showed that repeat stenting with DES to treat DES ISR provided better results compared with balloon angioplasty[21]. However, the implantation of a new DES raised concern related to the presence of multiple layers of struts in the vessel wall and the risk of stent thrombosis and recurrent restenosis. DEB have been suggested as an alternative approach to treat DES ISR[22], and data from randomised controlled trials suggested that DEB are superior to balloon angioplasty and similar to first-generation DES[23]. Moreover, in the RIBS III study there was a suggestion that the use of second-generation DES was superior to first-generation DES; also, the use of intracoronary imaging was associated with better long-term outcomes[20,24]. In particular, a meta-analysis by Palmerini et al demonstrated that, among the second-generation DES, durable fluoropolymer-based CoCr-EES were associated with the lowest rates of long-term adverse events and maximum efficacy[25].

Finally, in keeping with previous studies, diabetes mellitus was the only predictor of recurrence of MACE after DES ISR treatment[26,27]. The development of drug-eluting stents has significantly improved the results of percutaneous revascularisation among diabetic patients, but a number of challenges remain, including higher rates of restenosis and stent thrombosis. Stent implantation in a coronary artery induces an inflammatory response, including mobilisation of progenitor cells and ingrowth of smooth muscle cells. Diabetic patients have accelerated neointimal hyperplasia and high rates of subsequent restenosis after stent placement[28], resulting from neointimal hyperplasia mechanisms including increased TGF-ß signalling and a direct influence of hyperglycaemia on smooth muscle cell migration[29]. Restenosis is more common after placement of longer stents or in arteries with smaller diameters, and diabetic patients more frequently present longer, more complex coronary artery lesions, and smaller reference vessels[30]. Taken together, these factors contribute to higher rates of restenosis when compared to non-diabetic patients.

A previous study by our group confirmed these observations, reporting that diabetic patients exhibit substantially more severe coronary atherosclerosis than non-diabetic patients at the time of a first acute coronary event, suggesting a more severe coronary atherosclerosis that may lead to late ISR[31]. The present study confirms that ISR after DES implantation is not a benign condition because it may lead to myocardial infarction in 10% of cases[32], and the re-restenosis rate remains relatively high, independent of the treatment modality used[33].

Two main implications arise from the present study. Firstly, as patients with early DES restenosis more frequently had an acute coronary syndrome as clinical presentation at the index procedure compared with late DES restenosis, they may need more aggressive medical surveillance that may allow an early diagnosis of stent failure. Secondly, our observation of a similar outcome among patients with early vs. late ISR regardless of the treatment for DES ISR (repeat stenting with DES or DEB) results in a new finding, but suggests, at the same time, the need for further study to understand which should be the treatment of choice for ISR.

Limitations

We acknowledge some limitations in the present study. Firstly, the study design is not that of a randomised study but rather of a hypothesis-generating registry with a relatively limited sample size. Secondly, patients did not have coronary angiography performed after ISR treatment, so we cannot exclude that some recurrent ISR might have been missed. Thirdly, no intracoronary imaging technique was mandated to guide ISR treatment. Fourthly, the majority of DES were first-generation DES, which are not used any more, thus it remains undetermined whether the same findings apply to second-generation DES. However, it remains of great interest to investigate the long-term consequences of first-generation DES implantation. In addition, due to the lack of intracoronary imaging at the time of ISR, the potential different mechanisms of ISR in first- and second-generation DES remain unknown.

Conclusions

The LATE DES registry showed that patients with early DES restenosis, compared to patients with late DES restenosis, more frequently presented with an ACS at the index procedure; however, the two groups did not differ in terms of the occurrence of MACE after ISR treatment at one-year follow-up either with DES or with DEB. Diabetes was the only independent predictor of MACE.

Impact on daily practice

Both early and late ISR are still observed in the real world, especially when complex coronary lesions are faced. The LATE DES registry showed that patients with early DES restenosis more frequently had an acute coronary syndrome (ACS) as clinical presentation at the index procedure compared to those with late DES restenosis. This may suggest a closer medical surveillance in ACS patients to allow an early diagnosis of stent failure, especially in diabetic patients. Diabetes, in fact, was the only independent predictor of MACE after ISR treatment in the present study.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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